ECONOMIC EVALUATION OF BIOLOGICAL THERAPY USE AMONG PATIENTS WITH CROHN'S DISEASE

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ABSTRACT

DAVID B. WEI: Economic Evaluation of Biological Therapy Use
among Patients with Crohn's Disease
(Under the direction of Dr. Joel F. Farley)

Crohn's disease (CD) is a chronic inflammatory disorder that substantially impairs quality of life for patients and entails enormous economic burden to the US society. Biological therapies can effectively treat Crohn's disease. The treatment strategy of using biological therapy for CD is currently shifting from the conventional 'bottom-up' approach that reserves biological therapy as the last medical resort to a more aggressive 'top-down' approach that endorses early use of biological therapy. This dissertation sought to evaluate the impact of this shift in treatment on healthcare utilization by CD patients and healthcare costs to payers.

First, we examined healthcare utilization and costs for CD patients in a large claims database dating from 2005 to 2009. We found that early biological users had lower utilization of inpatient services and higher prescription drug costs than late biological users. Annual medical costs for both biological user groups were comparable. We constructed a decision tree model and conducted budget impact analysis to predict the financial ramifications for third party payers of the change in prescription drug costs resulting from top-down treatment approach. Our results showed that the top-down approach of biological therapy was associated with increased prescription drug costs in the first year of disease. Incremental drug costs from top-down approach were significantly reduced in the second and third years

following CD diagnosis. Last, we conducted a cost analysis to compare total healthcare costs for patients who adopted biological therapy following top-down or bottom-up approach. We found that patients following the top-down strategy incurred higher healthcare costs in the first year of disease. In the second and third years, the top-down strategy appeared to be cost neutral, which was mainly attributed to a cost reduction in non-drug services.

In conclusion, novel biological therapies have been increasingly used among CD patients, and the new top-down treatment strategy can affect allocation of healthcare costs. Top-down treatment approach resulted in higher prescription drug costs for patients, especially in the first year of disease, when compared to patients following the conventional bottom-up approach. The top-down strategy for CD is projected to be cost neutral in the long term.

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LIST OF ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
aTNF	Anti-tumor necrosis factor
BIA	Budget impact analysis
CCAE	MarketScan Commercial claims and encounters database
CCI	Charlson Comobidity Index
CD	Crohn's disease
CDAI	Crohn's disease activity index
CEA	Cost-effectiveness analysis
CI	Confidence interval
COB	Coordination of Benefits
CPI	Consumer price index
CUA	Cost-utility analysis
DSA	Deterministic sensitivity analysis
ER	Emergency room
FDA	Food and Drug Administration
IBD	Inflammatory bowel disease
ICD-9	International Classification of Disease, 9th revision
IRB	Institutional Review Board
GEE	Generalized estimating equations
GI	Gastroenterology
MCO	Managed care organization
PBMO	Pharmacy benefit management organization
PPO	Preferred provider organization
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year

CHAPTER I:

INTRODUCTION

1.1 Overview

Crohn’s disease (CD) is a chronic inflammatory disorder that affects around a half million Americans.[1] Despite its relatively low prevalence compared to other common gastrointestinal disorders, CD substantially impairs quality of life for patients and entails enormous economic burden to the US society.[2] In 2006, total direct medical costs were estimated at $18,000 per patient and over $10 billion to the US healthcare system.[3] Prescription drug expenditure accounted for the largest proportion of medical costs (35.3%) in 2003, an increase of almost 25% since 1990's.[4-6] Costs for prescription drugs may increase even more with several novel drug therapies entering the market that are FDA-approved for clinical use.

Biological therapy is a novel drug class approved by the FDA for treatment of Crohn’s disease. Biological agents (including infliximab, adalimumab, natalizumab and certolizumab pegol) are clinically effective for moderate to severe disease, resulting in rapid onset of mucosal healing, better quality of life, and maintenance of remission.[7-9] The beneficial effects of these biological therapies have resulted in a notable change of CD treatment options since the approval of infliximab (Remicade®, Centocor) by the FDA in 1998.

Prior to the era of biological therapy, first-line treatment for patients with moderate and severe disease consisted of low-dose steroids and/or antibiotics, then followed with azathioprine and 6-mercaptopurine (6-MP) as maintenance therapy. These traditional therapies were not clinically satisfactory, and often caused serious side effects. As many as 75% of CD patients required surgery for management of their disease after failing to respond to these pharmacological therapies, and more than 40% of CD patients needed subsequent surgeries.[10]

With a growing number of new biological agents under investigation, these biological drugs play a more important role in the therapeutic regimen for Crohn's disease. Biological therapies have proven to be potent and effective disease modifiers, and are widely prescribed to CD patients. However, treatment strategy has been under debate in recent years as clinicians determine the optimal stage of the disease to introduce biological therapy. Under current Crohn's disease management guidelines, biological therapies are generally reserved for patients who fail to respond to first-line therapy.[11] This conservative approach entails starting treatment with conventional drugs, then moving to more advanced biological therapies as the disease progresses. This approach, referred to as 'bottom-up' therapy, has long been the mainstay of clinical practice with regard to biological therapies for CD patients. A new and more aggressive approach promotes the use of biological therapies at the early stage of disease before patients become glucocorticoid dependent and possibly even before glucocorticoid treatment is initiated. This approach, noted as 'top-down' therapy, has gained more popularity in recent years. Clinical evidence from newly published studies has shown that patients adopted biological therapies early in disease course had experienced superior mucosal healing, more rapid remission, and a higher rate of remission when compared to the

late adopters.[12, 13] It is believed that the early use of biological therapies may alter natural disease progression, and provide great benefits to patients. Thus, the treatment paradigm for Crohn's disease is currently shifting from the conventional bottom-up approach to a more aggressive top-down approach.

Despite their clinical efficacy, innovative biological therapies are associated with substantial drug cost. The annual drug costs of biological therapies are three to four times higher than conventional, non-biological drugs.[10] Because treatment strategy for CD is shifting to include biological therapies in the first-line treatment, a surge of biological therapy use is anticipated in the next few years. This rapid increase of high-cost medications raises concerns about the extent of reimbursement that payers will provide for these drugs in the long term. To contain healthcare costs, payers may practice a variety of strategies, including prior authorization, closed formulary, tiered copayments and coinsurance.[14] These policy changes can potentially affect the access to these novel drugs, and limit the therapeutic benefits to patients in need. Therefore, in order to understand the financial implication to payers, it is imperative to study the economic outcomes of CD patients due to the shifting treatment strategy.

In the literature to date, no studies evaluated the economic outcomes for CD patients during the transition of treatment strategy changes from bottom-up to top-down approach. Recent economic studies have commonly used cost-utility or cost-effectiveness analysis (CUA/CEA) to demonstrate the value of novel biological therapies, but the validity of the data sources is questionable, providing limited generalizability and usefulness. The cost data were outdated and did not account for the increasing trend of drug cost and new biological therapies approved for CD treatment in recent years. Additionally, the effectiveness data

were often based on the results from clinical trials, instead of 'real-world' patient data. In this dissertation, I will take a real-world data approach based on a large administrative database to assess the economic impact from the top-down therapy for CD.

1.2 Specific Aims

A potential surge in the use of biological therapies among CD patients due to the treatment strategy change from bottom-up to top-down approach raises concerns about the affordability and sustainability of third party payers, and, in the long run, the well-being of CD patients. To cope with the overwhelming financial burden, payers may potentially change their policies, thereby limiting patients access to novel biological therapies. Lack of information about the economic outcomes from CD patients hinders further research regarding the affordability and sustainability of payers in the healthcare system. In this dissertation, I will evaluate the effect of this treatment strategy change on : a) the short-term and long-term economic outcomes of CD patients; b) payer's affordability, determined by conducting a budget impact analysis, and c) long-term sustainability, assessed by conducting a comprehensive cost analysis. To ensure the validity of these analyses, this dissertation will use a real-world large database that contains healthcare service information for millions of patients over time. From this large database, two comparison cohorts will be formed according to their clinical utilization data in recent years: a) bottom-up users with late adoption of biological therapies; b) and top-down users with early adoption of biological therapies. The economic outcomes of both patient cohorts are evaluated annually based on claims data from 2005 to 2009, and will be used to estimate their outcomes in the first three years following CD diagnosis. Economic evaluations for payers, including a budget impact

analysis and cost analysis, will be based on the predicted outcomes of CD patients. The specific research aims are as follows:

Aim 1: To estimate the utilization and costs of healthcare services used by CD patients, and to compare the utilization and costs between early and late biological users

This aim will be addressed by analyzing the commercial medical and pharmacy claims of CD patients from 2005 to 2009. Utilization and costs associated with different healthcare services, including inpatient hospitalization, outpatient visits, emergency room visits and prescribed medications, will be extensively examined. More specifically, utilization rates and costs of healthcare services will be compared between different CD patient cohorts, which are designated below.

Cohort Comparison 1: Biological Therapy Users vs. Non-Biological Therapy Users

Patients will be classified as biological therapy users if they used any amount of biological therapies following a confirmed diagnosis of CD. Non-biological therapy users are CD patients who used no biological therapies at any time during the course of their disease. For each year from CD diagnosis, healthcare utilization and costs in these two patient groups are summarized for comparison.

Cohort Comparison 2: Top-down Biological Users vs. Bottom-up Biological Users

Biological therapy users are categorized according to their treatment strategy. Under conventional bottom-up approach, biological therapies are reserved as the last pharmacological resort after patients failed in other pharmacotherapies, including 5-aminosalicylic acid (5-ASA), 6-mercaptopurine(6-MP) and glucocorticoids. Thus, patients who used biological therapy following any conventional non-biological drugs are considered

bottom-up biological users. Top-down biological users are those who directly used any biological therapy in the first line treatment.

<u>Aim 1a</u>: To calculate the utilization and costs of healthcare services for all CD patients by cohort from 2005 to 2009

Descriptive statistics will be calculated for healthcare utilization and cost variables for CD patients in four different cohorts according to the claims data from 2005 to 2009. Healthcare utilization is measured by the following outcome variables: number of outpatient visits, number of inpatient visits, total length (in days) of inpatient stays, number of emergency room visits, and number of prescriptions. Healthcare costs include the total amount paid by payers in the following service sectors: outpatient visits, inpatient visits, emergency room visits, and prescription medications.

<u>Aim 1b</u>: To compare utilization and costs between early and late biological users from 2005 to 2009, and estimate the utilization and costs for patients in both cohorts in the first three years of disease

Multivariate regression models are employed to examine all individual utilization and cost variables between top-down and bottom-up biological users. The between-group differences will be adjusted by a number of covariates, including patient characteristics, health plan type and healthcare service provider types. The patient characteristics in the regression model include demographic characteristics (age, gender, race, region, and insurance coverage), and patient's general health condition (comorbidity). Health plan type contains patients' healthcare insurance information, including health plan type (PPO, POS, and HMO). Healthcare service provider characteristics include provider specialty. The following outcomes will be calculated: a) the differences in healthcare service costs between

early and late biological users - the economic outcomes for the new treatment strategy change; b) the differences in prescription drug costs between the two biological user groups in the first year of disease - the short-term economic outcome; and c) the differences in overall healthcare services between the two groups in the coming three years - the long-term economic outcome. Predictions for both short and long-term economic outcomes are provided in subsequent economic evaluations under Aim 2 and Aim3.

<u>Aim 2</u>: To assess the impact of short-term economic outcome for CD patients on third party payers based on the changing treatment strategy for disease management

Based on the prediction of short-term economic outcomes for CD patients in both early and late biological users, a budget impact analysis (BIA) will be used to estimate the financial implications of the new CD treatment paradigm to third party payers, in particular, the prescription drug expenditures to pharmacy benefit managers (PBMs) in managed care organizations (MCOs). The change in prescription drug costs from the current late adoption treatment approach to the new early adoption approach will be predicted for the first year of disease, and the second and third years of disease as well. A decision tree will be constructed to compare the accumulated prescription drug costs, including costs for biological therapies, between these two treatment approaches. In addition, probabilistic sensitivity analyses will be performed to examine the robustness of the estimation from the variation of input parameters. The result of the budget impact analysis can be used by PBMs to forecast the incremental cost or savings in the first three years of disease due to the changing treatment strategy.

<u>Aim 3</u>: To evaluate whether or not the top-down approach for CD management is more cost-saving than the bottom-up approach for third party payers when accounting for the long-term economic outcomes of CD patients

To address this aim, the costs associated with a broader range of healthcare services, including inpatient visits, emergency room (ER) visits, outpatient visits, and prescription drugs, will be collectively examined to determine whether or not the new treatment paradigm is cost-saving in both the short (one-year) and long (three-year) term. A decision tree is designed to model the two treatment approaches according to disease severity and treatment response.

An accurate assessment of budget impact from the aggressive top-down treatment approach can facilitate third party payer decisions regarding whether or not formulary changes are needed to cope with the change of treatment strategy. Unfavorable modifications to the formulary could prevent patients from accessing the novel therapy, and further reduce their well-being in the long term. A reliable prediction of the impact on total medical costs can inform payers, as well as healthcare administrators and providers, regarding the long-term benefits associated with the top-down approach.

1.3 Dissertation Outlines

Following the Introduction (Chapter I), Chapter II provides further background information and a systematic review of related literature. In Chapter III, theoretical and conceptual frameworks are established, and Chapter IV provides a detailed discussion of the research methods. Chapters V, VI and VII are each dedicated to one research manuscript. Study findings and limitations are summarized in Chapter VIII.

CHAPTER II:

BACKGROUND AND LITERATURE REVIEW

This chapter consists of two sections. The first section provides the background information related to Crohn's disease, including disease epidemiology, disease management, medical treatments, and economic data. The second section is a rigorous review of related literature.

2.1 Background

2.1.1 Disease Epidemiology

Crohn’s disease (CD) is a major inflammatory bowel disease (IBD) that can affect any portion of the gastrointestinal (GI) tract from the mouth to the perianal area, but primarily the small intestine and colon.[10] The disease is relapsing and characterized by diarrhea, abdominal pain, fatigue, fever, clinical symptoms of bowel obstruction, and passage of blood and mucus. Patients may also develop strictures, abscesses, or fistulas.[15] This chronic GI disorder affects around a half million Americans with incidence rate at 5.8/100,000 person-year and prevalence rate of 144/100,000.[1, 16] The peak incidence of CD occurs in patients between the ages of 15 and 25 years.[17] With regard to gender, more

studies show a male predominance. [18] The risk for Crohn's disease is influenced by genetic factors, and elevated by cigarette smoking, however, the etiology and pathogenesis of CD remain obscure.[19] Crohn’s disease continues to be among the most challenging chronic illnesses in clinical practice.[20]

2.1.2 Disease Morbidity and Mortality

Crohn's disease is characterized with an elevated mortality rate and significant morbidity. Population-based epidemiological studies showed that the mortality rate of CD is 20-70% higher than that in the general population.[21, 22] Recent studies reported that exposure to new biological therapy, such as infliximab, did not significantly change the mortality rate and relative risk of death. The mortality rate was 0.53 per 100 patient-year for patients who were treated with infliximab, a biological drug, which is similar to 0.43 for those who were not.[23, 24]

Surgery is inevitable for the majority of CD patients after all other medical interventions have failed. Cohen et al. reported that 79% of CD patients will need surgery at some point in their lives, and 45% of these patients require a second surgery. The annual rate of surgery recurrence is 8-10%.[10]

Corticosteroids are only used for patients with more severe disease, particularly those requiring hospitalization due to potential side effects and long-term dependency. Therefore, use of corticosteroids is an important indicator of disease severity. A population-based study reported that 43% of patients from Olmsted County, Minnesota used steroids.[25] Two studies conducted in Europe showed that higher percentages of patients have used steroids.[26, 27]

2.1.3 Disease Management

At present, CD is neither medically nor surgically curable. Therapeutic goals for CD are to induce and maintain disease remission, improve quality of life, and minimize long-term effect from toxicity and complications.[11] Although the disease management plan for individual patient is tailored according to his or her response and tolerance to medical interventions, disease severity, disease location, and disease-related complications are the key factors prompting medical and surgical treatment decisions in clinical practice. Severity of Crohn's disease is often measured by the Crohn's Disease Activity Index (CDAI), a research tool quantifying symptoms. The CDAI consists of eight clinical components, such as the number of liquid or soft stools each day for seven days. Each component is weighted based on a point system, and the CDAI is the sum of all points for each component. According to the CDAI score, disease severity is separated into four categories: a) asymptomatic remission (CDAI<150); b) mildly to moderately active (CDAI 150-220); c) moderately to severely active (CDAI 220-450); and d) severe-fulminant (CDAI>450). Generally, the therapeutic approach consists of the following sequential steps: a) treat acute disease; b) induce clinical remission; c) maintain response/remission; and d) if necessary, surgery. However, medical therapy can be quite different depending on disease severity.[11] Mild to moderate active disease is commonly treated with oral mesalamine or sulfasalazine daily. Moderate to severe disease is often treated with prednisone daily. Azathioprine, 6-mercaptopurine (6-MP), and methotrexate are prescribed for steroid-induced remission or steroid-refractory disease. Anti-TNF monoclonal antibodies can be considered for patients who have not responded to corticosteroids and immunosuppressive agents. For patients with severe or fulminant disease, higher doses of corticosteroids, broad-spectrum antibiotics, and

immunosuppressants (e.g., tacrolimus) are indicated. Surgical intervention is recommended for patients who have failed to respond or experience worsening symptoms. Below are the current guidelines for patients with mildly to moderately active and severe Crohn's disease.[11]

2.1.4 Medical Therapies

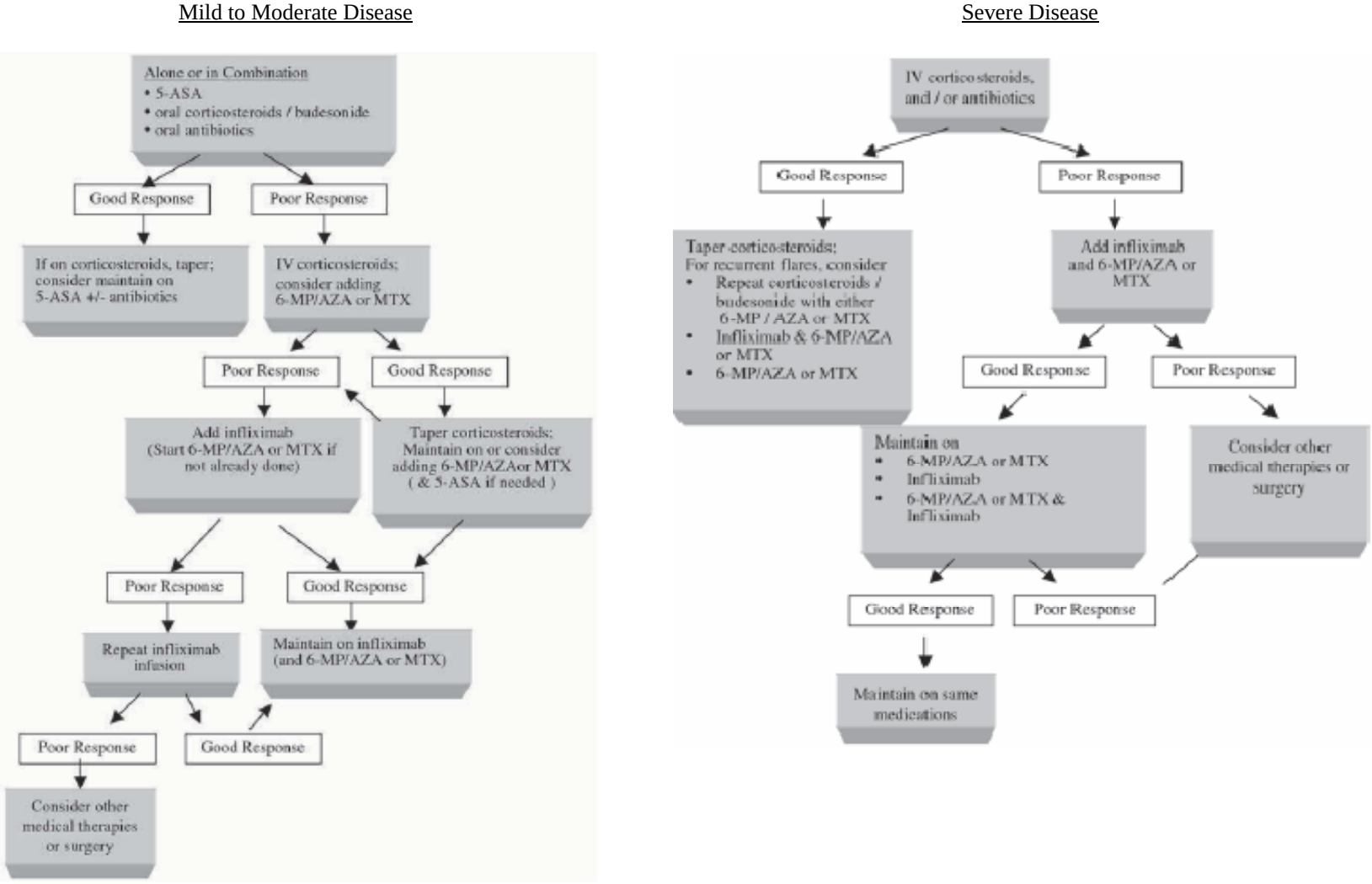
Aminosalicylates (sulfasalazine or mesalamine) are the most common drugs prescribed for Crohn's disease to prevent or control inflammation. In patients with mild to moderate disease activity, aminosalicylates have been shown to be effective up to 80% of the time. The primary active component is 5-aminosalicylic acid (5-ASA). Most of 5-ASA drugs (eg. sulfasalazine) are delivered to the colon, so the aminosalicylates are more effective for patients with active colonic or ileocolonic disease, but are relatively ineffective for patients with isolated small bowel disease. The 5-ASA drugs have a number of side effects, and are not helpful in patients with more severe disease.

Antibiotics (ciprofloxacin or metronidazole) are suggested when aminosalicylates can not control symptoms.

Steroids (prednisone or budesonide) are used to treat the disease if symptoms persist. Steroids can not achieve long-term remission, and are associated with a large number of side effects, and can cause dependency.

Immunomodulators (azathioprine, 6-MP, methotrexate) are used as maintenance therapy to keep patients in remission, however, the overall response rate is not satisfactory.

Figure 2.1 Bottom-up Treatment Guidelines



Source: Lichtenstein et al, *Management of Crohn's disease in adults.* Am J Gastroenterol, 2009.

Biological therapies (infliximab, adalimumab, natalizumab, and certolizumab pegol) are biological therapies that have demonstrated efficacy in multiple clinical trials for patients with moderate to severe Crohn's disease.

Immunosuppressants (cyclosporine, tacrolimus) are occasionally used to treat CD patients who have not responded to conventional drugs (e.g., steroid resistance). Concerns about their long-term toxicity (especially high risk of renal injuries) have restricted the use of immunosuppressants to CD patients.[28]

2.1.5 Biological Therapy

Conventional drug therapies for CD treatment, including 5-ASA, corticosteroids and immunomodulators, have a relatively low response rate and only 50% of patients achieve sustained remission. Those treatments also cause many side effects, such as toxicity from corticosteroids and cytopenia from azathioprine.[29, 30] Although the etiology of CD remains unclear, dysregulated immune responses are believed to play an important role in the process of CD development.[31] Monoclonal antibodies can be specifically designed to modulate immune cell proliferation and, indeed, biological therapies that target immune pathways have emerged as a novel and effective therapeutic class for many immune mediated disorders, including rheumatoid arthritis, psoriasis, cancer, and Crohn's disease. For example, infliximab, adalimumab and certolizumab pegol are anti-tumor necrosis factors (Anti-TNFs). They can inhibit over production of TNF, which is an important pro-inflammatory cytokine involved in the pathogenesis of Crohn's disease.[32] Four biological therapies have been approved by the FDA for treatment of Crohn's disease.

Infliximab (Remicade®) is a chimeric monoclonal antibody directed against tumor necrosis factor (TNF)-α that has shown efficacy in the treatment of patients with moderately to severely active Crohn's disease that fail to respond to other treatment options or those with fistulising disease. Infliximab treatment is generally initiated with a single intravenous infusion at a dosage of 5 or 10 mg/kg as induction therapy, and followed by repeated doses every four weeks at a dosage of 5 mg/kg to sustain clinical remission.

Adalimumab (Humira®) is a recombinant human IgG1 monoclonal antibody specific for human TNF. In randomized clinical trials, a greater percentage of patients treated with 160/80 mg of adalimumab achieved induction of clinical remission versus placebo after four weeks of treatment. A greater portion of patients, who experienced a clinical response after induction treatment, achieved clinical remission with a dose of 40 mg in the bi-weekly maintenance group compared to the placebo maintenance group. Adalimumab is administered by subcutaneous injection, and initial dose (Day 1) was 160 mg, followed by 80 mg two weeks later (Day 15). At Day 29, patients began a maintenance dose of 40 mg every other week.

Natalizumab (Tysabri®) is a recombinant humanized IgG4κ monoclonal antibody produced in murine myeloma cells. The safety and efficacy of natalizumab were evaluated in three randomized trials. Induction of clinical response was assessed at Week 10 in the first trial, and at Week 8 and 12 in the second. Maintenance of response was evaluated at Months 9 and 15 in the third trial. The recommended dosage is 300 mg intravenous infusion in every four weeks.

Table 2.1 Biological Therapies for Crohn's disease

Brand Name	Generic Name	Manufacturer	FDA Approval	Dosage & Route	Co-Indications
Remicade®	infliximab	Centocor	8/24/1998	Intravenous Infusion, 5mg/kg at 0, 2, and 6 weeks, then every 8 weeks.	Ulcerative Colitis, Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis
Humira ®	adalimumab	Abbott	2/27/2007 (12/31/2002 for RA)	Subcutaneous Injection, 160 mg on Day 1, 80 mg on Day 15, 40 mg every 2 weeks.	Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis, Juvenile Idiopathic Arthritis
Tysabri ®	natalizumab	Biogen Idec and Elan	1/14/2008	Intravenous infusion, 300 mg, every 4 weeks.	Multiple Sclerosis
Cimzia ®	certolizumab pegol	UCB	4/22/2008	Subcutaneous injection, 400 mg at weeks 2 and 4, then 400 mg every 4 weeks	Rheumatoid Arthritis

Source: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ (Labeling information)

Certolizumab pegol (Cimzia®) is a recombinant, humanized antibody Fab' fragment with specificity for human tumor necrosis factor alpha (TNF-α). The efficacy and safety of certolizumab pegol were assessed in two randomized clinical trials. Compared to patients in the placebo group, a greater proportion of certolizumab pegol-treated patients achieved clinical response at Week 6 (induction) and Week 26 (maintenance). The recommended initial adult dose of certolizumab pegol is 400 mg (given as two injections), and following by the same dose at Weeks 2 and 4. In patients who exhibit a clinical response, the recommended maintenance regimen is 400 mg every four weeks.

A growing number of new biological therapies are under investigation. More biological therapies may be approved by the FDA and added to the therapeutic pyramid for the treatment of Crohn's disease.

The advent of new drug therapies has not only brought more treatment options to patients, but has also changed the landscape of the treatment strategy. All four biological agents (see Table 2.1) demonstrated therapeutic benefits to patients in multiple clinical trials.[7-9] These benefits included: a higher response rate in the induction for patients with more severe disease, rapid onset of clinical response within 2 weeks, greater effectiveness in maintaining long-term remission, and significant improvement in health-related quality of life. Due to the lack of a long-term safety profile, however, the use of novel biological therapies has been controversial in clinical practice in recent years.

2.1.6 Revolution of Disease Treatment Approach

The introduction of biological therapies in the past decade has resulted in considerable changes in the Crohn's disease treatment paradigm. Prior to the approval of infliximab, therapeutic options for CD patients were limited. Most patients underwent surgeries once they failed to respond to conventional treatments. While novel biological therapies have been prescribed to patients with active Crohn's disease, treatment algorithms emphasizing on the optimal time to introduce biological therapies have been evolving as more efficacy data become available.

The conventional treatment approach advocates biological therapies as the last medical resort. Biological therapies are generally used in patients who are refractory or

intolerant to conventional drugs. This so-called 'bottom-up' or 'step-up' approach has been recommended in most CD management guidelines worldwide. Toxicity, immunogenicity, and lack of efficacy data about biological therapies as first-line treatment have been major concerns that limit their use for CD patients.

A new and more aggressive ‘top-down’ treatment approach has gotten considerable attention from inflammatory bowel disease (IDB) specialists.[33] Early introduction of biological therapies into the CD treatment regimen can increase their therapeutic benefit, partly by changing the natural course of disease progression. Compared to the bottom-up approach, the top-down therapy introduces biological therapies as first-line treatment, either in combination with immunomodulators or as monotherapy alone. A flow chart depicting both treatment approaches is shown in Figure 2.2.

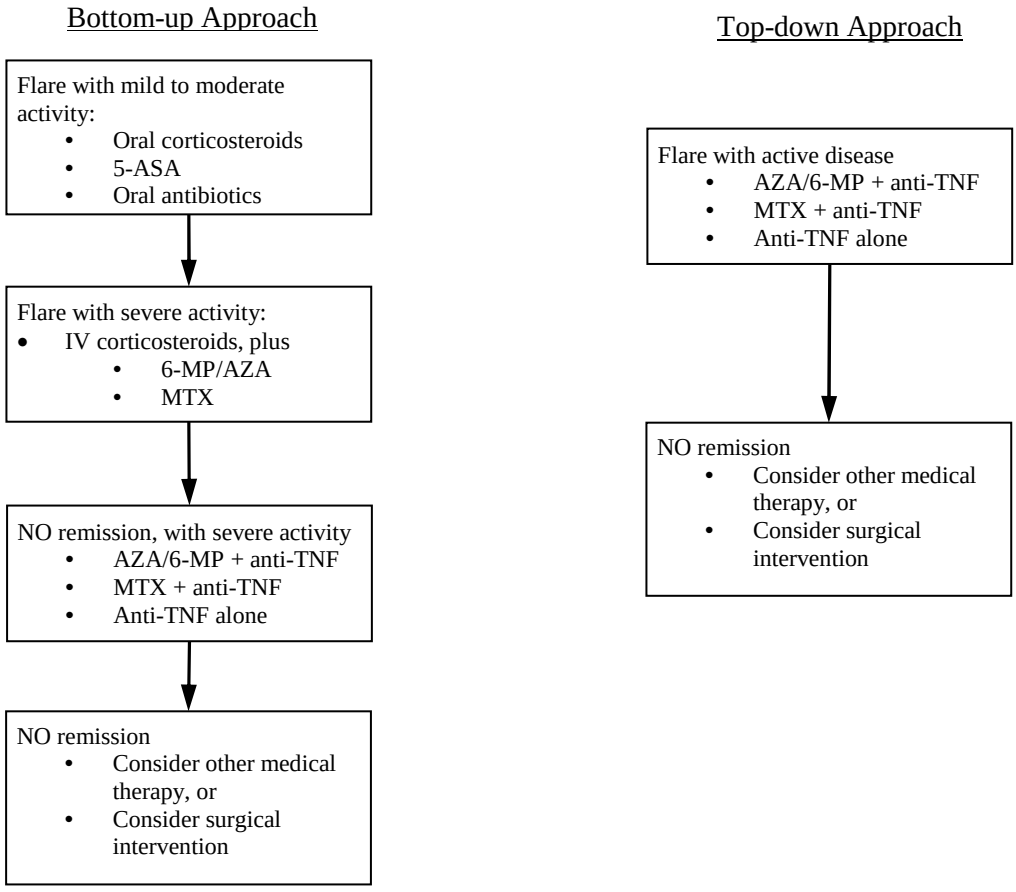
Two recent studies, SONIC[1] for infliximab[12] and an open randomized study [13], have shown that the top-down approach is superior to the bottom-up approach among CD patients who were naïve to steroids and biological therapies. Study treatment arms including patients who received biological therapies early in course of their disease were found to have a more rapid remission and higher remission rate than those who received standard therapy. Evidence in these two recent studies will substantially change the perspective of the use of biological therapies. The treatment paradigm for Crohn’s disease is shifting from the conventional therapeutic algorithm to early aggressive treatment approach.

In regards to the notation of CD treatment strategy, 'bottom-up' (or 'step-up') and 'top-down' are frequently used in the literature to represent the conventional and early aggressive approaches respectively. These notations are rather conceptual with no consensus about their

[1] Study of Biologic and Immunomodulator Naive Patients in Crohn's disease (SONIC) was a Phase III trial comparing infliximab and infliximab and azathioprine in the treatment of Patients with Crohn's disease.

definition in clinical practice. In this dissertation, we simply consider patients who adopted biological therapy early in disease course as top-down users, and those who used biological therapies later after attempting conventional drugs as bottom-up users.

Figure 2.2 Comparison of CD Treatment Approaches



2.1.7 Economics of Crohn's Disease

In 2007, U.S. healthcare spending increased by 6.1 percent to $2.2 trillion, or $7,421 per person. The healthcare portion of the gross domestic product (GDP) reached 16.2 percent.[34] Despite its relatively low prevalence compared to other common GI disorders, CD substantially impairs quality of life for patients, and entails high morbidity and

enormous economic burden.[2] The average annual direct cost of healthcare per patient was estimated at $8,727 in 1992[4], $12,417 in 1994[5], and $8265 in both 2003 and 2004[6]. Although the annual direct cost was relatively stable, the cost distribution for different healthcare services has changed significantly. In 1992 and 1994, drug costs only accounted for a small percentage of the total direct costs, and were 4.6% and 3.5%, respectively. Hospital costs contributed to the majority of expenses at 55.8% in 1992 and 57.3% in 1994.[4, 5] In both 2003 and 2004, pharmaceutical claims accounted for the largest proportion of direct cost (35.3%), then followed by hospitalization (31.4%).[6] This drastic change in cost distribution is primarily attributed to the emergence of biological therapies for the treatment of CD in the past decade. The annual drug cost, including the drugs themselves, as well as drug administration and wastage, was estimated at $17,176 for adalimumab-treated patients, and $18,214 for infliximab-treated patients in 2007.[35] With the treatment strategy shifting from the bottom-up to the top-down approach, biological therapies will be used among a larger portion of patients, and will likely be used for long-term maintenance. A massive increase in the use of these expensive drugs will add to the financial burden for third party payers and patients. However, these highly effective drugs might potentially be cost-saving if patient utilization of health care resources is reduced. For example, a study conducted with the CD population at the University of Chicago showed that one year's use of infliximab was associated with significant decreases in many areas, such as: surgery (38%), gastrointestinal surgeries (18%), endoscopies (43%), radiographs (12%), ER visits (66%), and hospitalizations (59%).[36] This dissertation is therefore enlightened to overcome the lack of information about long-term economic value of novel biological therapies.

In addition to direct medical costs, indirect costs can constitute a substantial portion of total costs incurred by Crohn’s disease. Indirect costs include expenses associated with disability, days off from work, transportation, and time spent with family. It has been estimated that 5-10% of CD patients each year are unable to work.[4] There is great anticipation that the clinical effectiveness of novel biological therapies will be translated into a substantial reduction of disability and overall indirect costs.

2.2 Literature Review

2.2.1 Overview

In this section, peer reviewed journal articles from the past fifteen years are rigorously reviewed for the development of this dissertation. This review focuses on the following major areas corresponding to the research aims: a) use of biological therapies among Crohn's disease patients; b) healthcare costs related to Crohn's disease; and c) economic evaluation of biological therapies targeted for the treatment for Crohn's disease. After a thorough review of the literature, research gaps in each targeted area are identified, which support the research aims of this dissertation.

2.2.2 Use of Biological Therapies in Crohn's Disease Patients

Conventional medical therapies (including aminosalicylates, corticosteroids, antibiotics, and immunosuppressors) for Crohn's disease can help patients achieve and

sustain remission only 50% of the time, and entail serious side effects.[32] In contrast, biological therapies (e.g., infliximab and adalimumab) have proven to be novel and effective nonsurgical treatment in clinical trials, and have been prescribed to Crohn's disease patients.[37] However, under current CD management guidelines, the mainstays of medical therapy for active disease are corticosteroids, antibiotics for fistulized disease, and immunosuppresants when patients are steroid-dependent or steroid-refractory. Biological therapies are reserved as the last medical resort, and are limited to patients with severe symptoms. To have a better understanding of how patients and clinicians adapted to these innovative therapies, a literature review was conducted utilizing a PubMed search and the following key words: *((use) OR (utilization)) AND ((biological) OR (infliximab) OR (adalimumab) OR (tumor necrosis factor)) AND (crohn's).* Only four studies were identified involving information about the use of biological therapies in CD patients from 2000 to 2010 (see Table 2.2).

Results of the literature search were inadequate and inconsistent. Only two studies were conducted with the US patient populations, and one of them used a small sample from a Veterans Affairs (VA) medical center. Due to the differences in patient cohorts and study time frames, the proportion of patients who used biological therapies in these studies is notably different. Hilsden et al. conducted a national survey in 2001 on all members of the Crohn's and Colitis Foundation of Canada. Among 1,787 CD patients, nearly 6% of them reported having used infliximab, even though the survey was conducted three years after approval of the drug. Patients with more severe disease, as evidenced by increased hospitalizations, surgeries, and steroid use, were more likely to receive infliximab (21.1% for severe disease, 5.4% for moderate disease, 2.3% for mild disease, and 1.8% for patients with

inactive disease). Patients between age of 16 and 24 had the highest use of infliximab (11.6%), and older patients (age > 55 years) were least likely to use infliximab (2.7%). Significant differences in infliximab use based on region of residence, gender, and income level were not observed.[38]

Table 2.2 Studies Related to the Use of Biological Therapies in Crohn's Disease Patients

Study	Setting	Findings	Limitations
Hilsden 2003	1,787surveyed in Canada in 2001	6% of patients used infliximab; younger patients used more. Variations in infliximab use based on region of residence and income were not seen.	Canada study, early days, descriptive analysis
Jewell 2005	205 patients in a retrospective audit at 7 centers in UK	72% of patients received one infusion initially; 19% of patients received 6-month infusion.	UK sample in different healthcare system, small sample, and short follow-up (6 month) period
Pressman 2008	2,964 patients from a community setting, cohort study from 1998 to 2006	494 (16.7%) initiated infliximab, younger patients used more. Infliximab use continuously increased. High discontinuation rate	Community setting, matching algorithm by outpatient visits
Feagins 2010	127 patients from VA medical center; retrospective cohort study	Biologic use varied inversely with age of onset. 55.5% at 21, 0% for >70yrs	VA setting, small sample, majority of patients were male,

Jewell et al. assessed infliximab use via a retrospective study that was undertaken at seven medical centers in the U.K. between August 2002 and September 2003. Among 205 patients with moderate and severe Crohn's disease, the majority (72%) received a single infusion, 4% had two infusions, 23% had three infusions, and 19% of patients received infliximab continuously during the 6-month follow-up period. Since the primary objective of

the study did not include assessing the predicting factors of infliximab use, no further analyses were conducted.[39]

Pressman et al. undertook a retrospective cohort study to investigate the patterns of infliximab use among CD patients in a community setting. The study population consisted data from 4,780 patients in Kaiser Permanente database from 1998 to 2006, and 537 (11.2%) of these same patients received infliximab at any time during the study period. In a cohort study, the case cohort included 494 patients who began receiving infliximab and met enrollment criteria. The control cohort was randomly chosen from the non-infliximab users, matched by the number of outpatient visits in the preceding quarter at a ratio of 1:5 (e.g., 1 case to 5 controls). The authors found that 29% of patients began receiving infliximab during a hospitalization. Significant predictors of infliximab use were age, number of inflammatory bowel disease (IBD) drugs, and comorbidity (Charlson Comorbidity Index). Gender, race and ethnicity were not statistically significant predictors. The authors also noticed that a large number of patients received only a single infusion of infliximab, i.e., 18% of patients in the overall population. High discontinuation and low drug persistency appeared to have controversial effects on healthcare utilization, which includes surgeries, hospitalizations, and immunomodulator use. It was also reported that the number of infusions for CD patients has been rapidly increased, and had not leveled off by the end of the study. The percentage of infusions that occurred in outpatient setting increased from 50% in 2001 to 97% in 2006.[40]

More recently, Feagins et al. conducted a retrospective review of the Dallas V.A. IBD database. They identified 127 veterans with CD from 2000 to 2008 and, for each identified patient, demographics (e.g., age, race, and gender) and disease characteristics (e.g., disease duration, location, disease behavior, and drug use) were obtained from his or medical records.

Overall, 34% of patients received treatment with a biological agent. Among younger patients (<21 years old), 55.5% used biological therapies, whereas no patients >70 years of age used these novel treatments. Use of biological therapies varied inversely with age at disease onset. In addition, disease severity and inflammatory arthritis had significant association with the use of biologics. There were no significant differences in disease duration, smoking status, and comorbidity.[41]

In summary, the literature provides some important information regarding the use of biological therapies in Crohn's disease patients. Biological therapies have been increasingly prescribed to patients with severe Crohn's disease. In addition to disease severity, younger age and comorbidity of arthritis contribute to patient use of biological therapies. There are also several significant limitations with these studies. First, patient samples of these studies were based on small (Feagins), regional (Pressman), or non-US populations (Hilsden and Jewell), which hampers generalization of results into the larger U.S. population. Second, with the exception of the small study conducted with veterans (Feagins), these studies took place during the early years of biologic availability. The results from Pressman and others cannot be extrapolated to recent years without mentioning several study limitations. Pressman's study failed to take into consideration the important fact that adalimumab was approved by the FDA in 2007, and both natalizumab and certolizumab pegol were approved in 2008, offering more biological treatment options to CD patients. Third, there are some serious methodological issues with these studies. None of these studies established an analytical model upon any theory, so their analyses were primarily data driven. Many important factors, such as insurance status, were not controlled. In Pressman's study, a matching algorithm

based on the number of outpatient visits is insufficient when controlling for potential confounders between patients groups.

In order to obtain valid information about the use of biological therapies among CD patients, we plan to conduct a cohort study (Aim 1) that is based on a large sample containing real-world data for more than seventy million insured individuals from 2005 to 2009, and employs a rigorous analytical model based on economic and behavioral theories.

2.2.3 Costs of Crohn's Disease

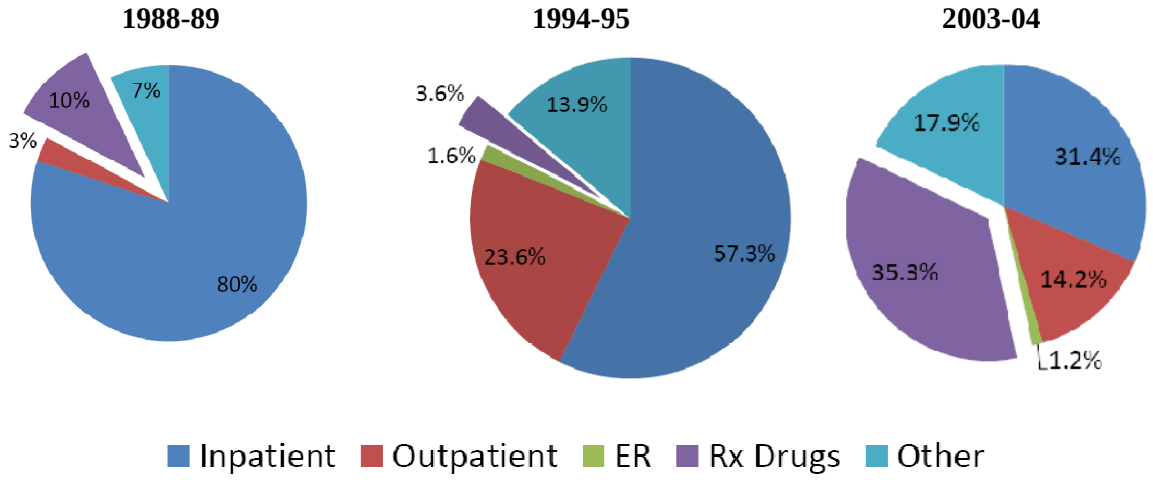
Crohn's disease is characterized by a high disease morbidity and financial burden to patients and society. The prohibitive costs of Crohn's disease are attributable to several factors: a) disease onset in early life; b) increased needs for surgical resections; and c) high drug costs. The U.S. economy is still recovering from a recession, and healthcare costs are under more scrutiny than ever. In order to better understand the economic burden of Crohn's disease and, more specifically, the medical costs and trend of medical costs among CD patients, I conducted a literature search in PubMed. Several important studies were identified that provided cost information specific to Crohn's disease in the U.S. spanning the past two decades (see Table 2.3).

The annual direct medical costs incurred by CD patients were high, and relatively stable from the 1990s to the early 2000s. The total annual cost was $6,561 in 1988-89[4], $12,417 in 1994-1995[5], $10,952 in 2003-2004[6], and $18,962 in 2005[42]. When adjusted for inflation according to the medical consumer price index, total annual costs of $6,561 in 1988-89 and $12,417 in 1994-95 became equivalent to $14,670 and $18,253 in 2005. Due to different methodologies and source data among these studies, these estimates appeared

inconsistent but can be useful in demonstrating the gross change in overall cost. Both infliximab and adalimumab are very costly, as a result, the trend in direct medical costs may have changed in recent years because biological therapies have been more frequently prescribed to CD patients. Ollendorf et al. estimated that the average cost for infliximab was $2,793 per infusion.[43] Kane et al. reported that the annual medical costs for patients treated with infliximab were $36,675, including a cost of $25,284 for infliximab alone.[44] Sandborn et al. estimated that the annual medical costs can be as high as $32,688 for CD patients receiving adalimumab weekly or every other week.[45] No recent studies have reported the direct medical costs of Crohn's disease in the U.S. This, it is imperative for third-party payers in the private sector or in the government healthcare system to know total medical expenditures for CD to facilitate budgeting and planning.

While total direct medical costs stayed relatively stable, the distribution of costs for different healthcare services has changed significantly. The proportion of costs attributable to inpatient and surgical services decreased from nearly 80% in 1988-89, to 57% in 1994-95, and further down to 31% in 2003-04. At the same time, the proportion of costs for outpatient medications drastically increased from 4% in 1994-95 to 35% in 2003-04.[5, 6] The shifting pattern of medical costs from inpatient services to outpatient medications has occurred with the simultaneous entry of biological therapies into treatment regimen for CD patients. It is believed that the increasing expenditure on pharmaceuticals, especially novel biologics, has offset the costs of hospitalization and surgeries.[46] However, there is a lack of evidence supporting this hypothesis. In clinical trials, biological therapies have demonstrated a lower utilization rate of inpatient services, but the results have not been confirmed in large, population-based studies over time.[47]

Figure 2.3 Comparison of Proportions of Medical Costs of Crohn's Disease



$6,561 in 1989	$12,417 in 1995	$10,952 in 2003
$12,205 in 2010*	$19,345 in 2010*	$13,470 in 2010*

Source: Hay et al, 1992; Feagan et al, 2000; Kappelman et al, 2008
* Adjusted with annual inflation rate at 3%

While previous research provides evidence about overall medical costs and distribution of costs for different healthcare services, there are still several important, unanswered questions regarding cost trends and patterns in recent years, as well as the cost difference between biological therapy users and non-biological therapy users.

First, the trend of total medical costs for Crohn's disease in recent years is unknown. Gibson, Ollendorf, and Kappelman used different claims databases from 1999 to 2005 in their studies, so little is known about the trend of total medical costs after 2005. While infliximab has continuously diffused into the clinical and patient communities, its use may have steadily increased in recent years. FDA approvals of adalimumab in 2007, natalizumab and certolizumab pegol in 2008 should also have boosted the use of biological therapies as more treatment alternatives became available to CD patients. In addition, the trend of medical expenditures for CD patients can be affected by changes in the healthcare system

and economic environment, such as the enactment of Medicare Part D in 2006 and the economic recession from December 2007 to June 2009. Medicare Part D may not have a direct impact on the majority of patients aged 64 or younger, with exception of those who are dually eligible for both Medicare and Medicaid. However, Medicare Part D can indirectly affect younger patients (<65 years) by influencing manufacturers' pricing strategy and third party payers' benefit structure. The economic recession could have greatly reduced patients' ability to pay for high-cost medications, such as biological therapies for CD treatment. In the U.S., the increase in total healthcare costs has appeared to slow down in recent years[34], but the trend in medical costs for Crohn's disease remains unknown.

Second, the distribution pattern of total medical costs in recent years is also unknown. It is impractical to extrapolate the empirical results based on data before 2005 to estimate the proportion of drug costs. The increase in drug expenditures may out-pace the costs of inpatient and outpatient services if innovative biological therapies are rapidly adapted by clinicians and patients. However, no confirmative data are available in the literature.

Third, the difference in total medical costs between biological therapy users and non biological therapy users is unknown. Studies in recent literature have paid little attention to differing the costs for these two subgroups of patients with Crohn's disease. The majority of studies summarized costs by services without delineating expenses for CD patients. While biological therapies are considered as the major contributor to total medical costs, little information is available about how much biological therapy users spent for different medical services, such as inpatient, outpatient, ER services as well as prescription drugs. The difference in costs between biological therapy users and those CD patients who have never used biological therapies, is also unknown. A fair comparison between biological users and

non-biological users may be hindered by confounding factors, such as disease severity. However, it is worth the effort to study the cost patterns between these two groups if their medical costs are categorically different. The difference in sub-groups among biological users is also worth noting. Persistent users (>3 months of continuous use) can experience increased medical costs than episodic users (occasional use of biological therapies). No information is available in recent literature about medical costs and cost patterns of patients in these two sub-groups.

In summary, while total direct medical costs have remained relatively stable in the past two decades, the proportion of costs associated with different services (e.g. inpatient hospitalization/ surgery, outpatient visits, ER visits, and prescribed medications) has changed. There has been a clear shift in medical spending from inpatient services to outpatient medications, which was presumably affected by the introduction of novel biological therapies. In the pre-biologics era, aminosalicylic acid drugs and corticosteroids were the mainstay of medical treatment for CD, with stable costs and cost proportions.[48] Since the first biological agent, infliximab, was approved by the FDA for CD patients' use, drug costs have increasingly accounted for a larger portion of total medical costs. Previous studies provided valuable information about the cost trend mentioned above, however, they have two important limitations: a) patient data utilized in these studies were prior to 2005, so little is known about the trend of total costs and cost patterns in recent years; b) no studies have compared costs and cost patterns between biological users and non-biological users.

Table 2.3 Summary of Studies Related to Costs of Crohn's Disease

Study	Setting	Perspective	Findings	Limitations
Hay 1992	Medical decision costing algorithm, augmented by 88-89 claims data	Health system	Total: $6561; Outpatient: $192; Diagnostic: $98; Inpatient: $5241; Rx: $671	Strong method but disease management out-dated.
Feagan 2000	607 patients from medical claims database from 10/94 to 9/95;	Payer & Patient	Inpatient: $7,115; outpatient: $2,936; MD office: $1,054; Rx: $444; ER: $202; Total: $12,417	Claims data, early years
Cohen 2000	147 patients in one hospital from 7/96 to 6/97	Hospital & Payer	charge: $35,378 (surgical 46,354; medical $20,744) Reimburse: 21,968 (Sur: 28,946, Med 12,666)	Sample from one institution
Ollendorf 2006	2230 CD patients treated with infliximab from Pharmetrics Claims database (6/00 to 12/03)	Payer & patient	Charge: $4441/infusion Paid: $2793/infusion	Commercially insured, early years of biologics, not per member cost
Gibson 2008	6569 CD patients from MarketScan claims data base from 1999 to 2005	Employers	Inpatient: $8679; Outpatient/MD: $7722; ER:$ 316; Rx: $2243.56 Total:$18,962	No data after 2005
Kane 2009	571 CD patients treated with 4+ infusions of infliximab from claims database (1999 to 2006)	Payer	CD-related costs: Inpatient: 2,185; Outpatient: $2,282; ER: $93;Rx (no inf.):$6,987;Rx (inf): $25,284 All-cause costs: Inpatient: $3,718; Outpatient: $5,383; ER: $258; Rx (no inf.): $11,391	Differentiate CD-related costs from all-cause cost. Unknown about the no-infliximab patients
Kappelman 2008	9056 CD patients + 24,829 controls from Pharmetrics claims database (2003 and 2004)	Payer	Total cost: $10,952 (CD); $2,898 (other) Cost diff (CD-control): Inpatient: $2,593 ER: $97; Rx: $2,919	Pediatric and adults mixed together; not current data
Sandborn 2011	260 CD patients received adalimumab EOW or weekly	Payer	$15,981 - 32,688	Adalimumab patients only

In this dissertation, we sought to comprehensively examine the direct medical costs incurred by Crohn's disease patients using a large and nationally representative database with healthcare utilization and expenditure data from 2005 to 2009. Analyses focus on trends and patterns of costs for CD patients in recent years, and the comparisons of cost trends and patterns between biological therapy users and non-biological therapy users. Based on recent data, we predict costs and trends for these groups in the first three years of disease, and conduct economic evaluations on prescription drug costs and total healthcare costs from the perspective of third party payers.

2.2.4 Cost-effectiveness of Crohn's Disease

Since the movement of evidence-based medicine in the mid-1980s, pharmacoeconomics has gained more and more popularity. In the past decade, pharmacoeconomic studies have been on the rise as third party payers faced budgetary issues due to the rapid growth of healthcare costs.[49] Crohn's disease is associated with a substantial financial burden to both patients and society at large. The financial burden is further increased when costly biological therapies became available for CD patients as alternative medical therapies. Due to the high costs and lack of sufficient safety data and clinical evidence, biological therapies have been fraught with controversies and critics.[32] Several pharmacoeconomic studies from the past ten years were identified after searching PubMed with the following key words: economic evaluation, cost benefit analysis, Crohn's disease, biological therapy, and anti-tumor necrosis factor. Study setting and the main results of these studies are summarized in Table 2.4. Most of these investigations made great effort

to demonstrate the cost effectiveness of biological therapies, mostly infliximab, among CD patients, and provided important information.

First, medical treatments with biological therapies, both infliximab (Remicade®) and adalimumab (Humira®), are associated with a very high incremental cost compared with the treatments with non biological therapy. In 2001, Arseneau et al. used Markov modeling to assess the cost-utility of infliximab by comparing infliximab combined with 6-mercaptopurine (6MP) and metronidazole (Met). The incremental cost-effectiveness ratio (ICER) ranged from $355,450 to $377,000 per quality-adjusted life-years (QALY) while infliximab was administered in combination therapies or as mono therapy. The findings of this early study indicated that infliximab interventions are more costly than other interventions that are already pricey, such as bone marrow transplant and peritoneal dialysis. Because clinical efficacy data were scarce, the ICERs were likely over estimated.[50] In 2003, the Health Technology Assessment program in UK reported that the cost per QALY in the treatment of chronic active Crohn's disease was £6700 ($10,953 in 2003 U.S. dollar) for a single-dose treatment, £10,400 (or $17,002) for episodic re-treatment, £84,400 (or $13,798) for maintenance treatment, and £102,000–£123,000 (or $166,750-$201,080) for initial treatment of fistulising disease.[51] Since the economic model was based on information submitted by the manufacturer and effectiveness data were obtained from randomized clinical trials (RCTs), the above results are likely downward biased.[51] Jaisson-Hot et al. compared the cost utility between infliximab and surgery among patients with severe Crohn's disease. The ICERs varied from €63,700 (episodic re-infusions) to €762,245 (maintenance therapy).[52] In a more recent study, Lindsay et al. evaluated the cost-effectiveness of maintenance treatment with infliximab among patients with active luminal and fistulising

disease. Compared to standard care in 2008, the incremental cost per QALY gained was £26,128 ($48,397 in U.S. dollar) for luminal CD, and £29,752 ($55,110) for fistulising CD.[53] Similar results were obtained in Bodger's investigation, which compared infliximab treatment for one year with standard care. From a Markov simulation, the ICER was £19,050 per QALY gained.[54] In summary, the cost-effectiveness ratio of infliximab treatment to standard care was around $50,000 per QALY gained among patients with severe CD disease, and this cost-effectiveness ratio could be even higher among patients with mild to moderate Crohn's disease. According to the unofficial cost-effectiveness threshold of $50,000 per QALY gained in the U.S., infliximab treatments do not appear to be cost-effective.

Head-to-head comparisons of adalimumab with infliximab have suggested that adalimumab is more cost-effective than infliximab, but still not cost-effective in comparison to the cost-effectiveness threshold. Kaplan et al. compared the cost-effectiveness of adalimumab as rescue therapy with high dose infliximab among patients who failed to respond to low dose infliximab. The cost per patient was $35,908 per QALY for patients receiving a dose escalation of infliximab, and $23,782 per QALY for patients receiving adalimumab. Even though adalimumab showed favorable cost-effectiveness, the costs of adalimumab were still considerably high.[55] In a recent study by Yu et al., adalimumab was only marginally more cost-effective than infliximab.[35] Compared with standard care, the incremental cost per QALY gained was £16,064 ($25,148 in 2009 US dollar) in severe CD patients, and £33,731($52,806) in patients with moderate-to-severe disease.[15]

Second, most analyses were conducted from the perspective of a third-party payer or healthcare system. In principle, the societal perspective is generally considered most appropriate and comprehensive when framing pharmacoeconomic studies because it

encompasses all costs and health effects of an intervention regardless of who incurs the costs and who obtains the effects in the entire society.[56] However, there are many technical obstacles in accruing the effects and costs from all members in society, and in assessing the effects and costs quantitatively when conducting studies from a societal perspective. For example, indirect costs, such as productivity loss, are usually difficult to measure monetarily. More importantly, the perspective of economic evaluation should reflect the viewpoint of the key audience (e.g. healthcare decision makers) who are primarily intended to inform. The payer's perspective, either from a third-party payer or from national healthcare service, is common in economic studies conducted in the U.S. and abroad despite the differences in healthcare systems.[35, 50, 55] Compared to a broad societal perspective, a more narrow perspective can not only ease the determination of relevant healthcare services and costs, but also provide measureable values for decision makers. In this dissertation, I intend to inform the decision-makers who are responsible for budgeting health benefit plans in the third-party payers in the private sector of US healthcare system. It is not my intention, however, to inform the budget administrator of each individual health benefit plan. Instead, all health plans will be considered together as a single payer. The analyses in my dissertation will be based on the perspective of this joint single payer, which provides health benefits to all commercially insured non-elderly Americans.

While many economic studies have evaluated the cost-effectiveness of biological therapies in different patient groups using various analytic methods, (e.g. Markov modeling), and different data source, there are several important limitations that are worthy of comment:

1. <u>The effectiveness of medical interventions with biologics in CUA or CEA was assessed by using data from clinical trials.</u> As a result, the clinical effectiveness of biological

therapies was likely over-stated because patients enrolled in clinical trials are generally healthier. Also the assessment based on small samples in clinical trials can hardly be generalized to the CD patient population. Given the short follow-up time in clinical trials (6 months to 1 year), the long-term benefits or risks of biological therapies can not be evaluated accurately. It is interesting to note that the difference in utility values, the denominator of the incremental cost-effectiveness ratio, was small in several studies. For example, Yu et al. reported that utility indices for treatment with infliximab and adalimumab were 0.865 vs 0.851 respectively.[35] The small difference in these utility indices can increase the magnitude of the incremental cost-effectiveness ratio. This is a controversial issue with methodology of CUA or CEA.[56] If credible long-term effectiveness data are not available, CUA and CEA are not the ideal approach for evaluating the novel drug therapies.

2. Cost data are not up to date, or are not based on real-world data. Several studies approximated the costs by using cost information, such as wholesale acquisition costs in Redbook® (Thomson Reuters, Ann Arbor, MI), and average costs published in other studies. Only a few studies used patient level data to calculate direct medical costs. Bodger et al. used data from the UK to derive total cost.[54] Yu et al. used patient level data in the US to estimate total costs, but patients were limited to the enrollees in the Medicare program.[35]
3. Selection bias and publication bias are threats to validity of the study results because of the influence from the sponsor in pharmaceutical industry. Most economic evaluation studies have been funded by the pharmaceutical companies, who are required to submit economic data about medical products to regulatory agencies in European countries for

market authorization. In the U.S., it is not mandatory for pharmaceutical companies to include the economic evaluation data as part of submission dossier. Thus, pharmaceutical companies have not incentive to conduct large scale economic studies, or publish those studies if the findings are not favorable to their products. Unsurprisingly, results in the literature unanimously favor therapies manufactured by sponsoring company, and against competing products. Due to this conflict of interest, economic studies purely designed as marketing tools by the pharmaceutical companies may not provide valid information to the public.

Because of a lack of data regarding the effectiveness of biological therapies among patients with Crohn's disease, we strive to evaluate costs associated with these biological therapies and, more broadly, the total medical costs of patients with Crohn's disease. Unlike existing studies in the literature, our research will use current patient level data from a large pharmacy and medical claims database to estimate costs from the perspective of third-party payers. With no conflict of interest to declare, we do not assume any proposition during the research.

Table 2.4 Summary of Pharmacoeconomic Studies Related to Crohn's Disease

Study	Setting	Perspective / Time Horizon	Findings	Limitations
Arseneau, 2001	CUA: inf vs. 6MP/met Markov modeling of 3 treatments Efficacy data: literature review Cost data: hospital billing	Third party payer, 1 year	ICER (3 tx vs. 6MP/met): Tx 1 (inf+6MP/met): $355,450 Tx 2 (inf): $360,900 Tx 3 (6MP/met+inf): 377,000	Efficacy data were scarce back in 2001; hypothetic interventions (eg. 3 infusions of infliximab).
Clark, 2003	Health Technology Assessment by NICE, revised from the company model in submission	UK NHS	Cost: £1,800 per dose CE: £6,700 for single dose, £10,400 for episodic retreatment, £84,400 for maintenance. (per QALY) Fistulizing CD, more costly	Strictly limit infliximab to severe patients, not for episodic treatment in UK setting
Jaisson-Hot, 2004	CUA: infliximab vs. surgery Markov modeling Efficacy data: literature+expert Cost data: literature	Payer, lifelong (2-month cycle)	ICER: (2 tx vs surgery): Tx 1 (relapse): €63,700 Tx 2 (maintain): €762,245	No patient-level data;
Kaplan, 2007	CEA: inf vs ada (rescue therapy) Decision tree modeling Efficacy data: clinical trials Cost data: literature, Redbook	Payer, 1 year	ICER: inf (5mg--> 10mg) vs ada $332,032/QALY	Not real-world data; only the sub-cohort lost response to 5mg/kg infliximab
Lindsay, 2008	CEA: inf vs standard care Markov modeling Data source: literature	UK NHS, 5 years	ICER (inf vs standard care): Severe luminal CD: £26,128 Fistulizing: £29,752	Sponsor funded, not based on patient data.

ada = adalimumab, inf = infliximab, TNF = tumor necrosis factor, WAC=wholesale acquisition cost, QALY=quality-adjusted life year

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Table 2.4 Summary of Pharmacoeconomic Studies Related to Crohn's Disease

Study	Setting	Perspective / Time Horizon	Findings	Limitations
Loftus, 2009	CEA: ada vs standard of care Efficacy data: clinical trials Cost data: literatures	UK NHS, 1 year	ICER (ada vs standard of care): Severe CD: £16,064/QALY Moderate-to-severe:£33,731/QALY	Abbott funded, not real world patient data, strong assumptions (perfect adherence, etc)
Bodger, 2009	CEA: inf / ada vs standard care Markov cohort analysis Efficacy data: clinical trials Cost data: UK patient-level data	UK NHS, 1 year	ICER (ada /inf vs Standard care): Inf (1yr, 2 yr): £19,050, £21,300 Ada (1yr, 2yr): £7,190, £10,310	Rigorous assumptions for Markov model, source of efficacy data
Yu, 2009	CUA: ada vs inf (maintenance) Efficacy Data: clinical trials (CHARM and ACCENT I) Cost Data: WAC, Medicare	Payer, 1 year	1-year remission: 47.2% vs 37.1% TNF cost: $17,176 vs $18,214 Total cost: $34,193 vs $39,045 QALY: 0.865 vs 0.851	Pharma (Abbott) sponsored, Small sample from clinical trials, Short time frame

ada = adalimumab, inf = infliximab, TNF = tumor necrosis factor, WAC=wholesale acquisition cost, QALY=quality-adjusted life year

2.2.5 Other Economic Evaluations of Crohn's Disease

In addition to cost-effectiveness studies, other formats of economic evaluation of drug therapies for Crohn's disease have been scarce in the literature. Although CEA has commonly been used to indicate value, researchers have also shown that CEA results are rarely used by decision-makers to inform formulary decision.[57] Budget impact analysis and resource consequence analysis are two complementary techniques that can be used to assess the impact of a new treatment on costs and resource use for a specific group of individuals.

Budget Impact Analysis

No budget impact analysis studies on biological therapies for Crohn's disease patients were identified in the literature search. However, budget impact analysis has been implemented in other disease areas. Sorensen and Andersen used this approach to assess the potential impact on the Danish healthcare budget of prescribing infliximab or etanercept for patients with rheumatoid arthritis.[58]

Resource Use Analysis

In 2002, Rubenstein et al. reported that infliximab decreases resource use among patients with Crohn's disease, and suggested potential cost savings. However, healthcare resources were not expressed in monetary terms, so the magnitude of cost saving is unknown.[36] Study patients (79 in total) were only followed for one year, and the long term effect on healthcare resources use was not addressed.

In 2007, Saro et al reported that infliximab appeared to be effective in routine practice by reducing hospital stays, but increased overall budgetary costs. However, the study sample was based on patients admitted to a single hospital in Spain, and the cohort of patients

receiving infliximab only included 34 patients. Thus, thus, the results can not be generalized to the larger US.S population.[59]

In 2009, Nugent et al conducted a population-based study of healthcare resource use among infliximab users beginning in 2001, and found that the number of physician visits, hospital visits, and surgeries was different between infliximab users and patients receiving other drugs.[47] This is the first population-based study to report resource utilization in multiple years under the 'bottom-up' treatment approach, however, these results are not easily translated into practice because resource use was assessed in natural unit of different healthcare service (e.g. number of hospitalizations), instead of a common monetary unit for comparison.

In 2010, Kappelman et al used a large claims database to estimate healthcare resource (inpatient, outpatient, ER, and endoscopy services) utilization occurring between 2003 and 2004, and found that utilization varied by gender, geographic region, and insurance type.[46] Although data analysis was not stratified by use of biological therapies, the study results still provided valuable information about the entire CD patient population.

In summary, the above studies prove that a budget impact analysis on medications and a cost saving analysis on resource use is feasible when using large administrative databases to evaluate the economic consequence of biological therapies under different treatment approaches. Kappelman et al showed that large administrative databases contain adequate information to investigate healthcare utilization. Additionally, Saro et al demonstrated that budgetary costs can be estimated when units of healthcare resources are priced correctly.[59]

2.3 Summary

The treatment strategy for Crohn's disease is now shifting from the conventional 'bottom-up' to a more aggressive 'top-down' approach, which promotes novel biological therapies as first-line treatment for CD patients. The rapid change in the treatment algorithm could extend greater clinical benefits to patients, but simultaneously incur greater financial burden for both payers and patients. Economic evaluation of novel biological therapies, especially during this transition period, is necessary. From recent literature, cost-effectiveness analysis studies did not demonstrate the value of these new therapies due to a lack of effectiveness data. Therefore, from the methodological point of view, it is more practical to conduct economic evaluations that focus on medical costs.

In this dissertation, budget impact analyses are used to evaluate the financial implications to payers by comparing the use of biological therapies under different treatment strategies. To the best of my knowledge, no budget impact analysis has been conducted to address costs related to the new treatment approach from the payers' perspective. Furthermore, a comprehensive cost analysis including all healthcare resources is conducted to evaluate the long-term sustainability of the new treatment paradigm by examining the difference in costs of healthcare resources between patients under the two different treatment approaches.

CHAPTER III:

THEORETICAL AND CONCEPTUAL FRAMEWORK

Modern research is often based on multiple theories from different disciplines. The theoretical framework encompasses the linkage between theories and specific research questions in a given setting. In this dissertation, Andersen's Behavioral Model of Health Services Use (Andersen's model), and Grossman's Model of Health Demand (Grossman's model) serve as the backbone for constructing the theoretical framework.

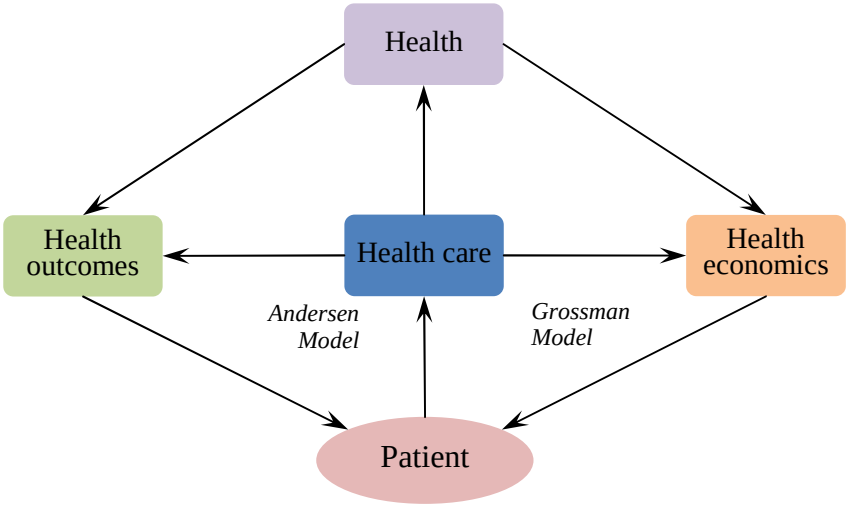
The conceptual framework outlines an operational roadmap for the research direction, and the relationships of different constructs. In this chapter, a conceptual framework is presented to demonstrate the theory-based approaches to addressing the proposed research aims.

3.1 Theoretical Framework

Important life goals for most individuals are to maintain or improve health status, and prevent injury or illness. While health is affected by any acute or chronic condition, it is natural for people to seek advice from healthcare professionals, and make use of healthcare facilities and services. Admittedly, all healthcare resources are not free and unlimited for all members to access, but rather, are constrained and shared in society. Therefore, using health

care is not only a process of health behavior undertaken to achieve optimal health status, but also a series of economic activities that produce health at certain opportunity costs. Health outcomes and economic consequences can reinforce or undermine the use of healthcare services. Figure 3.1 describes the relationships among health, health care, health outcomes and health economics. Andersen's Behavioral Model provides in-depth reasons as to why patients use health care from a health behavior point of view. Grossman's model purports that the ultimate purpose of using health care is to produce better health, and demand of health care is derived from the demand for health, and can be affected by many factors.

Figure 3.1 Theoretical Framework



3.1.1 Andersen's Model

Andersen's Behavioral Model of health services was developed in the 1960s. It has been widely utilized in the research of healthcare access and healthcare services utilization. The original model was designed to assist in understanding why families use health services,

define and measure equitable access to health care, and facilitate in developing policies to promote equitable access. After several revisions, the model, shown in Figure 3.2, incorporates the dynamic and recursive nature of health services.[60] The essence of Andersen's behavioral model is that the use of health services is a function of patient characteristics, which are delineated into three major components: a) predisposition to use services; b) factors that enable or impede use; and c) the need for care.

Predisposing characteristics refer broadly to everything that might predispose patients to need and use healthcare services. In Andersen's model, predisposing variables include demographic variables (age and gender), socio-economic status variables (education, occupation, race, ethnicity, etc) and health beliefs (attitude, value, and knowledge). These variables have proven to be risk factors for healthcare utilization, however, not all variables are readily available in the source data for secondary analysis. Among the predisposing characteristics, demographic and socioeconomic variables are usually collected in healthcare research databases, but variables representing health beliefs are often difficult to quantify and measure, even though health beliefs are believed to have substantial influence on patients' perception of need and use of healthcare services.

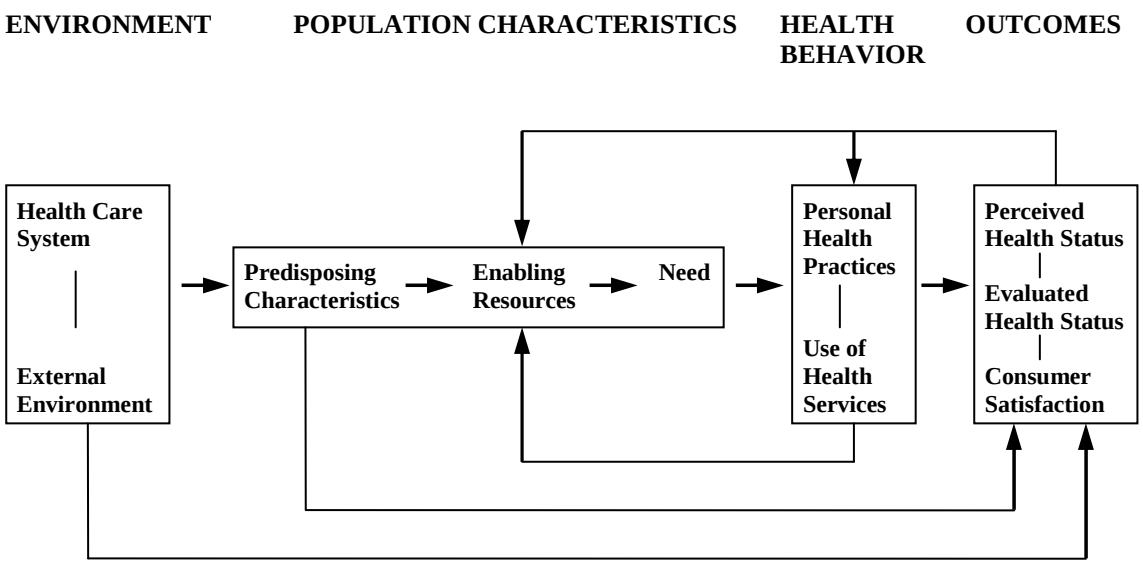
Enabling factors are variables that represent the adequacy of healthcare resource use. Healthcare resources include personal level resources (e.g., income, employment status, health insurance, and generosity of insurance coverage) and community level resources (e.g., per capita amount of healthcare personnel and facilities, and the quality of healthcare personnel and related facilities).

Need variables represent the necessity and importance of healthcare to patients. Needs can be self-perceived needs explained by social structure and health beliefs, or

evaluated needs judged by healthcare professionals regarding patients' health status. They are often the most immediate causes of healthcare service use.

In addition to the three major components listed above, Andersen's model also recognizes the external environment, both political and economic changes, as an important input for healthcare services. The model takes into account the influence of personal health practices, such as exercise, on the use of health services. Health outcomes, e.g., perceived and evaluated health status, in turn, can reinforce or impede the use of healthcare services.

Figure 3.2 Andersen's Behavioral Model



Source: Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? J Health Soc Behav 1995;36:1-10

3.1.2 Grossman's Model

Grossman's model is a theory of demand for healthcare with great influence from the health economics field. The basic model was developed in the 1970’s,[61] and revised to a more generalized model in the 1980’s.[62] Grossman used the theory of human capital to

explain the demand for health and healthcare, and show how consumers allocate resources for health. According to human capital theory, consumers invest in themselves through education, training, and health to increase their earnings. Since health can be capitalized, healthcare is demanded as a means for consumers to produce a larger stock of 'health capital'. Therefore, the demand for healthcare is considered to be a derived demand from the demand for health. This is the key element in Grossman's model.

In addition, the model also highlighted several other important aspects of health demand that distinguishes health and healthcare from other traditional goods. First, each individual is viewed as both a producer and consumer of health. Consumers do not merely purchase health passively from the market, but, instead, the consumer produces health, for example, by devoting time to health-improving activities. Second, health is treated as a stock which degrades over time in the absence of investments in health, so that health is viewed as a sort of capital. Third, healthcare is a consumption good that yields direct satisfaction and utility as well. It is also an investment good which yields satisfaction to consumers indirectly through increased productivities, such as fewer sick days, and better quality of life. In the health capital model, it is assumed that individuals inherit an initial stock of health that depreciates over time, particularly, at an increasing rate, after some stage in the life cycle, and can be increased by investment. The optimal level of health investment can be reached upon equilibrium where the marginal cost of health capital is equal to the marginal benefit from health outcomes. The following factors were found to be determinants of predicting the optimal level of health investment.

- Age: In general, the health of older people is likely to deteriorate faster than the health of younger people, so the optimal stock of health varies with higher

depreciation rates in later periods of the life span. Higher depreciation rates increase the cost of holding health capital stock. Therefore, elderly people purchase a greater amount of medical care, even as their health declines.

- Wage rate: The rewards of being healthy are greater for higher-wage workers, so increased wages will be likely to increase optimal capital stock. Higher wage not only implies increased return on health investment, but also implies increased opportunity cost in producing health.
- Education: Higher education is most often related to better health. Economists believe that education can improve the efficiency and productivity of health investment, so a given health investment can be generated at less cost for educated people. Educated people can better recognize the benefits of improved health and, thus, have a greater demand for health and healthcare.

While emphasizing the effect from age, education and wage rate, Grossman's model did not exclude the impact of environmental variables. Instead, the effect of other variables was hypothesized to be static. Grossman's model can help us identify key variables as determinants of the use of medical care, and understand how profoundly their effect can be expressed in mathematical terms.

3.1.3 Model Synthesis

In this dissertation, the research goal is to investigate the economic outcomes of CD patients while the treatment paradigm is shifting from the late to early adoption treatment approach. The effect of the treatment strategy change can be observed in greater utilization of

biological therapies and other healthcare services. Determinants of healthcare utilization can be conceptualized by the theoretical models discussed in the previous section. According to both Andersen's behavior model of health services and Grossman's model of demand of health care, the use of healthcare services among CD patients is determined by internal factors (e.g., patient's characteristics), and influenced by external factors (e.g., provider's characteristics and features of health plans provided by payers).

In the context of Andersen's model, the use of biological therapies is determined by three major categories of patient characteristics, including predisposing, enabling and need variables, and a number of external environmental factors. These external factors are often related to parties who have direct interaction with patients, including providers and payers. In clinical practice, major medical decisions are made jointly between patients, providers, and payers. Therefore, providers' characteristics, such as medical specialty, and features of health plans offered by payers (e.g., formulary and deductibles) are important external factors that influence on healthcare utilization.

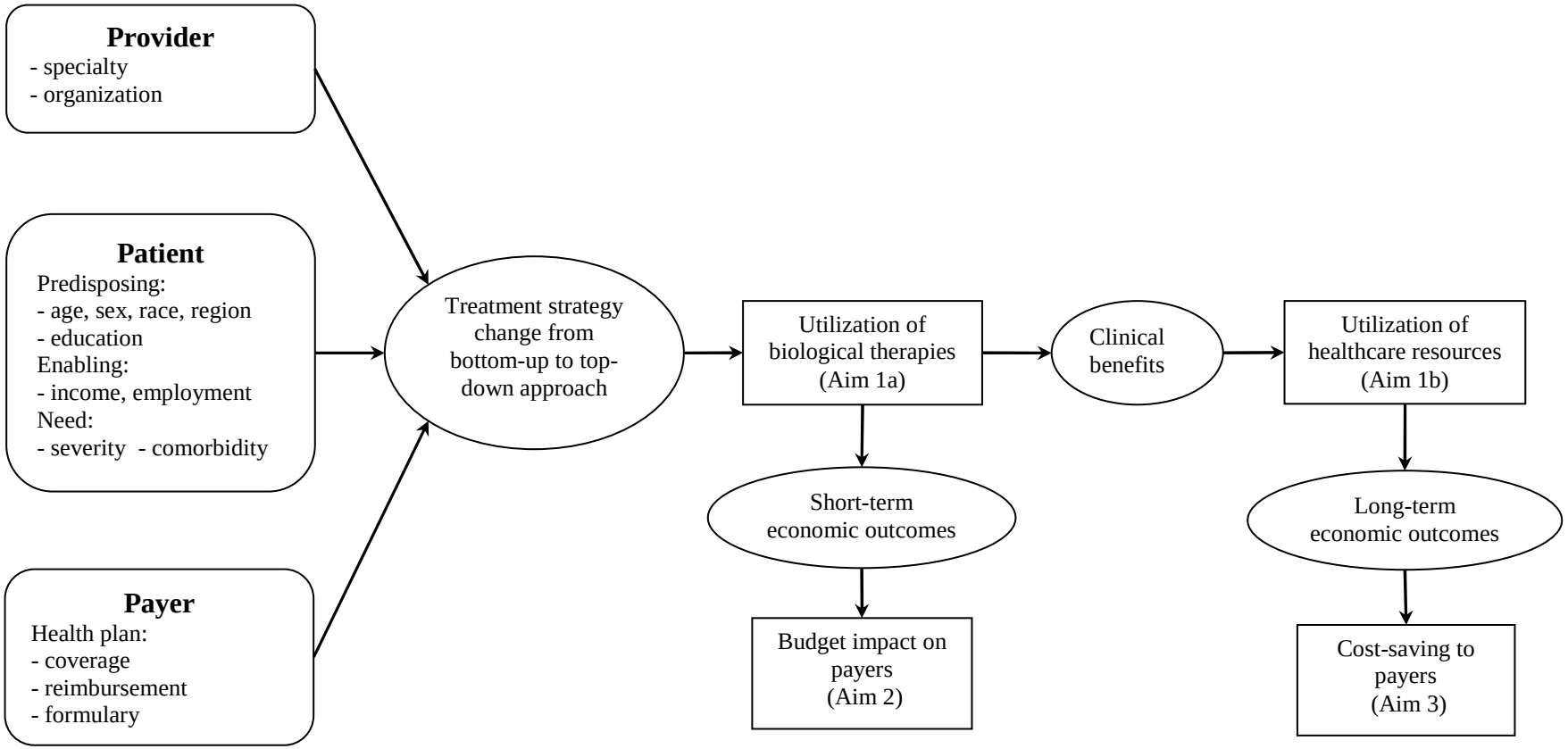
When considering Grossman's model, the use of healthcare services is mainly determined by the effects of age, education, and wage rate. Although Andersen's model has recognized these three variables as predictors of healthcare service utilization (e.g., age and education are predisposing variables, and wage is an enabling variable), no empirical information is provided to guide the analytic model construction. Grossman's model provides complementarily information about the effect as in mathematical expression, which suggests that predicting effects are likely non-linear and certain transformation may be needed in the model specifications.

3.2 Conceptual Framework

The theoretical models in the previous section provide the rationale and logic to determine why patients demand healthcare, how patients cope with their needs, and what factors can affect the decision to convert needs into health behavior. The conceptual framework for the current project, shown in Figure 3.3, presents a pictorial pathway of the research goals when the theories are implemented, and the relationships between causal factors. The research goals are to: a) investigate the impact of the treatment strategy change on the use of biological therapies in patients with Crohn's disease (Aim 1); b) estimate the change on economic outcomes of patients; and c) predict the financial impact on payers (Aims 2 and 3). The pathways in Figure 3.3 illustrate the following relationships:

1. The treatment strategy change from the bottom-up to top-down approach is the key environmental variable for CD patients that can directly impact the utilization of biological therapies, or indirectly influence CD patients via the providers. The top-down approach will increase the use of biological therapies among CD patients.
2. Besides the treatment strategy change, the use of biological therapies is also associated with patient's characteristics, and provider's characteristics, and features of health plans.
3. The short-term economic outcome of the treatment strategy change results from the increase in prescription drug costs since biological therapies are expensive medications.

Figure 3.3 Conceptual Framework



4. Clinical benefits of biological therapies will be reflected by a gradual decrease in utilization of other healthcare services, for example, fewer inpatient and ER visits. The long-term economic outcome of the treatment strategy change is the decrease of costs for other healthcare services.
5. Both short-term and long-term economic outcomes of the treatment strategy change for CD patients can have direct financial implications to payers. Short-term economic outcome about prescription drug costs can be used to predict the budget increase in the first year of disease, and long-term economic outcomes can be used to demonstrate whether or not the treatment paradigm change is cost-saving when drug costs are offset by a decreased use of other healthcare services after the first year of disease.
6. Financial implication for third-party payers can be related to the future formulary change, which can potentially affect the use of biological therapies by CD patients.

Based on the conceptual pathways, research for this dissertation will be conducted in the following steps.

1. The first part of this dissertation will focus on an empirical study of the claims database to determine the utilization of healthcare services, either prescription drugs alone or all healthcare services combined, among CD patients who are classified into different cohorts according to their use and usage pattern of biological therapies in previous years. The primary goal is to determine the differences in utilization between patients who are early and late biological users. Differences between these two patient cohorts will be adjusted using a wide range of covariates, which contribute to healthcare utilization according to the theories presented in section 3.1. Covariates include patient

characteristics (e.g., age, sex, race, ethnicity, region, education level, income, employment status, disease severity, and comorbid conditions), provider characteristics (e.g., treatment preference, specialty, and affiliated organization), and health plan features (e.g., coverage/generosity, reimbursement/copayment, and formulary). Admittedly, some variables, such as ethnicity, education level, income, and formulary, are not available in the primary data source (MarketScan claims database). Other variables, such as disease severity, and comorbidity, can only be approximated by healthcare utilization data records. Despite these limitations due to unobserved variables and potential misinformation, the covariates with adequate information in the claims database represent many important characteristics about patients, providers, and payers.

2. Next, the research focus shifts to the economic outcomes of CD patients. More specifically, I will predict both short- and long-term economic outcomes for top-down and bottom-up therapy users in three years following CD diagnosis by using empirical data from early and late biological therapy adopters in previous years (from 2005 to 2009). Short-term economic outcomes are represented by the prescription drug costs in the first year of disease. Long-term economic outcomes are represented by total healthcare costs, including expenditures for drugs, outpatient services, inpatient services, and emergency room services in the second and third years after CD diagnosis.
3. Lastly, the financial impact on payers will be estimated based on the aggregated economic outcomes of CD patients, who use either top-down or bottom-up strategy, at the population level. A budget impact analysis will be employed to predict the financial impact of top-down treatment approach on third party payers by comparing the short-term economic outcomes between top-down and bottom-up users of biological therapies

in the first year of disease. A cost analysis will be conducted to demonstrate the differences in total healthcare service costs for the long term.

3.3 Construction of Analytical Models

The conceptual framework guides the operation of this dissertation research by building the analytical models upon theories. These theories imply that patients' health behavior in healthcare utilization is largely determined by both internal (e.g., patient characteristics) and external factors (e.g., health plans provided by payers). Internal factors include three sets of characteristics: a) demographics (e.g., age, gender, race, and region); b) socioeconomic status (e.g., income, and education); and c) health status (disease severity, and comorbidity). External factors include the features of health plans (premiums, deductibles, formulary coverage, and copayments) and provider characteristics (specialty, knowledge, institution, and patient communication).

Patient Demographics

Both the Andersen and Grossman models suggest that age is a key determinant for healthcare demand and health behavior. Older patients incur a greater demand on health care, and likely use more healthcare resources. Crohn's disease is often diagnosed at a young age and does not significantly short the life span, so younger patients with CD may also sustain a high demand for health care. Gender, race, geographic region and urban residence are predisposing variables in the Andersen model, and are considered to be factors for predicting health demand in the Grossman model.

Socioeconomic Status

Income, education level, and ethnicity, are another set of important predisposing variables in Andersen's model. In economic models, income (i.e., wage rate) and education are two key factors that affect an individual's health demand. Higher income means greater ability to purchase better or more healthcare services. From an economic perspective, higher income gives people more incentive to improve or maintain their health by seeking healthcare resource or changing their lifestyle in order to keep well-paying jobs. Both behavioral and economic models assert that education is an important factor relevant to the need and use of healthcare. Higher levels of attained education can improve the efficiency of received healthcare. Educated people can better recognize the benefits of health and the value of healthcare, and seek more healthcare services. However, there is no socioeconomic status variable in the Marketscan claims database, so the socioeconomic variables are omitted in the analytical models.

Health Status and Disease Severity

In Grossman's model, current health status represents the initial health capital that patients inherit as baseline when determining their demand for healthcare in the future. In Andersen's model, health status is an important need factor that either stimulates or delays healthcare seeking. Patients with more severe disease symptoms and comorbid conditions are more likely to use increased healthcare resources.

Health Plan Features

Most people do not pay providers directly for health care, but instead, pay indirectly through health plans of insurance provided by insurance companies, or third party payers, which are either private financed systems or government subsidized public programs. Health plans, or

insurance plans, are designed with different benefit structures. Characteristics of health plans, such as premiums, deductibles, formulary coverage, and copayment, have financial implications that can affect the demand for healthcare, and subsequent health decisions. More generous health plans with low deductibles and low copayments can increase health demand and the likelihood of using healthcare.

Provider Characteristics

In the U.S., healthcare providers, mostly physicians, have a great deal of influence on patients' use of healthcare. Health decisions are often jointly made by patients and their providers. Providers' knowledge, specialty, affiliated institution, and patient communication style can have a substantial effect on the use of healthcare, and the level of usage.

3.4 Summary

Both health behavior and economic theories suggest that healthcare utilization is jointly determined by a wide range of internal patient characteristics and external factors related to payers and providers. These variables can be potential confounders, which need to be controlled for when examining the true effect of the treatment strategy change. The conceptual framework depicts the pathways and variable sources, and translates theories to an operational roadmap.

CHAPTER IV:

METHODS

This chapter presents the methodology applied to address the study aims for this dissertation, including the data source (Section 4.1), study sample (Section 4.2), study methods for Aim 1 (Section 4.3), study methods for Aim 2 (Section 4.4), and study methods for Aim 3 (Section 4.5).

4.1 Data Source

The MarketScan® Commercial Claims and Encounters Database (CCAE) (2005-2009) from Thomson Reuters (Healthcare) Inc. serves as the central data source for this dissertation. This database contains de-identified, person-specific health data including clinical utilization, expenditures, insurance enrollment/plan benefits, inpatient, and outpatient services, and outpatient prescription information. The data include over seventy million individuals, and include private sector health data from approximately 100 payers, and can be linked to track detailed patient information across sites and types of providers over time.

MarketScan CCAE is a major administrative database, and has been widely utilized by healthcare researchers to understand disease progression, treatment effect, healthcare utilization, health outcomes, and healthcare costs to patients, employers, and health plans.

4.2 Study Sample

All patients in the MarketScan CCAE database need to meet the following inclusion criteria for the study:

- A confirmed diagnosis of Crohn's disease, which requires at least one encounter from either an inpatient or outpatient setting with a diagnosis of Crohn's disease (ICD-9 codes: 555.0, 555.1, 555.2, 555.9) (Source: HCUP CSS tools for ICD-9-CM).
- Age between 18 and 64 (inclusive) at diagnosis of Crohn's disease. Older patients aged 65 and above are eligible for the Medicare program. Nearly 30% of children under age 18 are insured by public insurance programs like Medicaid and the State Children's Health Insurance Program (SCHIP). [63] Pharmacy and medical claims from elderly adults and children from low-income families, except those covered by supplemental insurance, are not included in the commercial claims and encounters database. As a result, only non-elderly adults are included in the study sample.
- At least two years continuous enrollment following the diagnosis of Crohn's disease between 2005 and 2009. More specifically, eligible patients are required to have at least six months of enrollment prior to their diagnosis of Crohn's disease, and have at least one year of enrollment after the diagnosis.
- Enrollee health plans must be network-based managed care programs, which can be one of the following: a) HMO (health maintenance organization); b) POS (point-of-service), c) PPO (preferred provider organization); and d) EPO (exclusive provider organization).

Patients meeting the following exclusion criterion are not eligible for the study:

- A diagnosis of any co-indicated condition where a patient used an FDA-approved biological therapy, including ulcerative colitis (ICD-9 codes: 556, 556.0, 556.1, 556.2, 556.3, 556.4, 556.5, 556.6, 556.8, 556.9), rheumatoid arthritis (ICD-9 codes: 714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 714.4, 714.81, 714.89, 714.9), ankylosing spondylitis (ICD-9 code: 720.0), psoriatic arthritis (ICD-9 code: 696.0), plaque psoriasis (ICD-9 code: 696.1), multiple sclerosis (ICD-9 code: 340), and juvenile idiopathic arthritis (ICD-9 code: 714.3) (Source: ICD9Data.com).

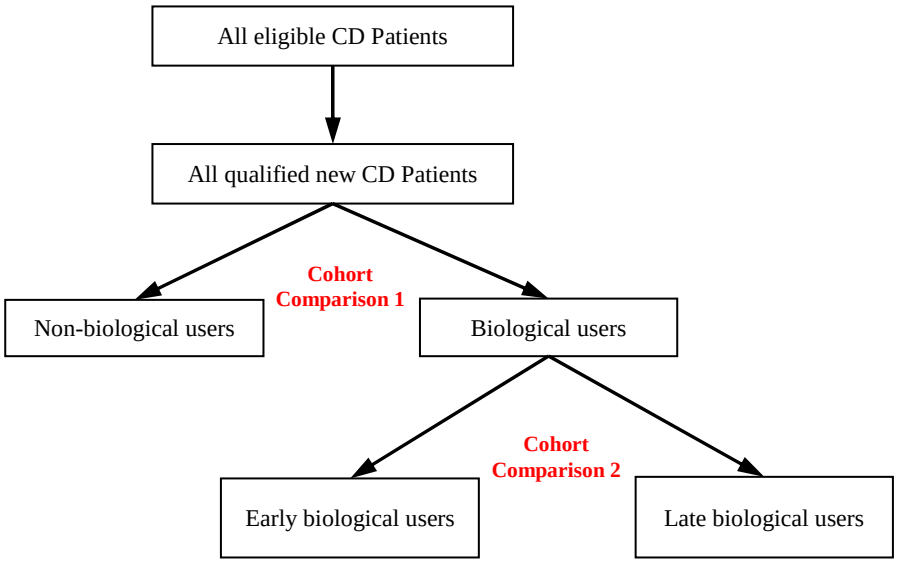
4.3 Study Methods for Aim 1 (cohort studies)

4.3.1 Study Cohorts

Healthcare utilization and costs for all eligible CD patients in the study sample are summarized annually to demonstrate trends from 2005 to 2009. In each year, utilization and costs are examined by healthcare service type, including inpatient services, outpatient services, emergency room services, and outpatient prescription drug use. Moreover, retrospective cohorts are constructed to compare healthcare utilization and costs associated with CD patients who are stratified by use and usage pattern of biological therapies in all years after the first confirmed diagnosis of Crohn's disease. A diagnosis was confirmed if at least one prescription of any essential CD drugs (listed below) was filled after a medical claim with CD as primary diagnosis. In addition to the inclusion and exclusion criteria

specified in section 4.2, CD patients are required to have a six-month washout period to fulfill new user design for this study. Under new user design, prevalent users with existing condition are excluded. To ensure a clean disease history, all eligible CD patients should be free of medical and pharmacy claims during the six-month washout period prior to the first CD diagnosis. Specifically, before their first CD diagnosis, patients are required to have no use of any essential CD drugs, including: a) aminosalicylates (i.e., sulfasalazine and mesalamine); b) antibiotics (i.e., ciprofloxacin and metronidazole); c) steroids (prednisone and budesonide); d) immunomodulators (i.e., azathioprine, 6-mercaptopurine, and methotrexate); e) biological agents approved for CD (i.e., infliximab, adalimumab, natalizumab, and certolizumab pegol); and f) immunosuppressants (i.e., cyclosporine, and tacrolimus). Two types of cohorts are designated for comparison as shown in Figure 4.1.

Figure 4.1 Sample Selection for Cohort Studies



Biological therapy users vs. non-biological therapy users

New CD patients are dichotomized into biological therapy users and non-biological therapy users, according to whether or not biological therapies were introduced into their treatment plan. Patients in the biological cohort are those who used any type of biological therapy after their first diagnosis date between January 1, 2005 and December 31, 2009. Non-biological users are those patients who have never used any biological therapies before and after the diagnosis date.

Early biological users vs. late biological users

Biological users are further divided into two sub-groups, early and late users, according to their treatment strategy. Early biological users are patients who used biological therapies as first-line treatment in the early stage of disease. Late biological users are those patients who used a biological therapy after any of, or a combination of, the following drugs: aminosalicylates, antibiotics, steroids, immunomodulators, regardless the amount of use. We presume that the early and late biological users followed the top-down and bottom-up treatment strategies respectively. The annual estimation of healthcare utilization and costs for both early and late biological users from 2005 to 2009 will be referenced in predicting the utilization and costs in the first three years of CD for the budget impact analysis (Aim 2) and cost saving analysis (Aim 3).

4.3.2 Outcome Variables

Outcome variables in the analysis are utilization of healthcare services and associated costs. Healthcare services include inpatient visits, outpatient visits, emergency room visits,

and outpatient prescription drugs. All-cause healthcare services of each type are inclusive when utilization and costs are calculated. No attempts are made to differentiate Crohn's disease related services and costs due to technical difficulties in separating these services from services for other conditions. Crohn's disease is often characterized by gastrointestinal involvement and extraintestinal manifestations (e.g., arthritis, eye involvement, skin disorders, malnutrition, etc.), and is often associated with significant co-morbid conditions, however, their causal relationship with CD is unclear.(www.uptodate.com) The treatments for extraintestinal and co-morbid conditions are not categorized as specifically related to Crohn's disease in the claims database. Thus, it is impractical to accurately group the claims into those related to CD and those that are not. Since the focus of this dissertation is to determine the financial impact of the treatment strategy shift on payers, overall medical costs are more meaningful than medical costs specific to CD. Lastly, the economic evaluation is based on the difference in costs for CD patients utilizing either early or late adoption of biological treatment approach. When all other variables are controlled for in the analyses, the economic impact can be attributed to the treatment strategy change. Thus, all-cause healthcare utilization and costs are the outcome variables for this dissertation.

For eligible CD patients in four different cohorts (i.e., biological users, non-biological users, early biological users, and late biological users), outcome variables are defined to constitute healthcare utilization and costs for each individual patient based on their claims data from 2005 to 2009. Three sets of outcome variables are used to quantify healthcare utilization: a) healthcare utilization variables, representing the quantity of individual healthcare services; b) gross cost variables, depicting the total healthcare costs for payers, patients (e.g., out of pocket costs), and coordination of benefits (COB); and c) net cost

variables, representing the costs for payers only. The definitions for outcome variables are provided below.

Healthcare Utilization Variables

- Total number of unique inpatient admissions
- Total length of stay (in days) for all inpatient admissions
- Total number of visits to a doctor's office or using other outpatient facilities
- Total number of emergency room visits
- Total number of outpatient drug prescriptions (including refills)

Gross Cost Variables

- Total gross payment for all inpatient services and admissions, including facility and professional payments
- Total gross payment for all outpatient services rendered in a doctor's office, hospital outpatient facility, or other outpatient facility
- Total gross payment for all emergency room services
- Total gross payment for all outpatient prescription medications, including mail ordered prescriptions
- Total gross payment for all inpatient, outpatient, emergency room, and prescription medication services

Net Cost Variables

- Total net payment made by third party payers for all inpatient admissions and services, including facility and professional payments
- Total net payment made by third party payers for all outpatient services rendered in a doctor's office, hospital outpatient facility, or other outpatient facility

- Total net payment made by third party payers for all emergency room services
- Total net payment made by third party payers for all outpatient prescription medications, including mail ordered prescriptions
- Total net payment made by third party payers for all inpatient, outpatient, emergency room, and prescription medication services

All outcome variables are standardized to annual rates or annual costs according to the amount of utilization or costs incurred from CD diagnosis date to the end of enrollment. Therefore, values of outcome variables are prorated by dividing by the number of enrolled months from CD diagnosis, then multiplying by twelve. All costs are adjusted with annual inflation rates for medical care, and expressed in 2010 US dollar ($).

4.3.3 Independent Variables

As the analytical models are constructed to compare outcomes between early and late biological users, the key independent variable is the user cohort indicator. The value of the indicator is set to '1' for patients in the early user cohort, and '0' for patients in the late user cohort.

Covariates are included in the analytical models to control for potential confounding effects. The following variables are designated as covariates in the analyses according to the theoretical framework (see Chapter 3):

- Age (at the year of diagnosis)
- Gender (female or not)

- Geographic region (northeast, north central, south, or west)
- Urban residence (metropolitan statistical area or not)
- Employment status of primary beneficiary (full time, part time, or others)
- Relationship to employee (non-dependent employee, or dependent)
- Size of employer (large US employer or not)
- Charlson Comorbidity Index (CCI) score (based on claims data in the washout period, six months prior to diagnosis)
- Number of prescriptions filled in the washout period, six months prior to diagnosis
- Health plan type (EPO, HMO, POS, or PPO)
- Principal provider specialty (gastroenterologist, or others).

4.3.4 Regression Models

In the cohort comparisons, multivariate regression models are constructed to evaluate the cross-group effect on healthcare utilization and costs while controlling for a variety of co-variates. The regression model is expressed in the following form:

$$Y = \beta_0 + \beta_1 X_{BioRx} + \beta_i X_{demog} + \beta_j X_{health} + \beta_k X_{ins-plan} + \beta_l X_{provider} + \beta_m X_{year} + \varepsilon$$

where Y is an outcome variable, Y_{BioRx} is a dichotomous key variable that indicates the treatment strategy of the use of biological therapies. X_{demog} represents a group of demographic variables (e.g., *Age*, *Gender*, *Region, MSA*, *Employ*, *LargeEmp*, and *EmpRel*), X_{health} represents health status (indicated by *CCI*, Charlson Comorbidity Index and *RxNum*, number of prescriptions used in the washout period (six months prior to diagnosis)), $X_{ins\text{-}plan}$

represents type of insurance plan (i.e., *PlanType*), $X_{provider}$ represents the characteristics of the provider (i.e., *Specialty*), X_{year} represents the number of years from 2005 to the observed year. The definitions for all predicting variables are provided in Table 4.1.

The generalized estimation equation (GEE) regression model is used to examine group differences in a series of outcomes variables (mainly costs, and number of events). The GEE model is an extension of the generalized linear model (GLM) to accommodate correlated data with a focus on estimating the aggregate response for the population.[64] The GEE model has been more and more frequently applied in cohort studies involving longitudinal data.[65] Empirically, GEE is most suitable for estimating the effect when outcome variables do not exhibit a normal distribution, and an unknown correlation is present. The outcome variables in this study can be categorized into two types, i.e., cost and event count. Cost data in healthcare are usually highly skewed from the normal distribution, often require transformation (e.g., log or inverse) before fitting regression models. Event count likely has a gamma or Poisson distribution. In the GEE model, the underlying data distribution of outcome variable can be specified by a suitable choice of the link function to fit the model. A test method developed by Park et al. can be used to facilitate the choice of link function.[66] For each outcome variable, observed values for the same patients in multiple years are likely correlated. GEE can easily handle the regression setting with longitudinally repeated measures. Therefore, the GEE model is used in this dissertation because it can analyze non-normal data and handle the within-patient correlation appropriately.

Table 4.1 Definitions of Independent Variables in the Regression Models

Variable	Type	Definition
X_{BioRx}	Key independent variable (Dichotomous)	1 for early users, 0 for late users
Age*	Numeric (continuous, or discrete)	Age of patient at initial diagnosis of Crohn's disease
Gender	Categorical (male, female)	Gender of patient
Region	Categorical (northeast, north, south, or west)	Geographic region
MSA	Dichotomous	Metropolitan statistical area: 1 = urban, 0 = non-urban
Employ	Dichotomous	1 for full time employment status, 0 for part time or others
EmpRel	Dichotomous	1 for non dependent employee, 0 for dependent
LargeEmp	Dichotomous	1 for large US employer, 0 for other health plans
CCI	Numeric, continuous	Charlson Comorbidity Index score
RxNum	Numeric	Number of Rx in washout period
PlanType	Dichotomous	1 for PPO, 0 for others (POS, HMO, EPO)
Specialty	Dichotomous	1 if principal provider is a GI specialist (STDPROV = 275), 0 for others
Year	Numeric	Number of years from 2005

* Age is also grouped as 18 to 39 years, and 40 years and above.

Multivariate logistic regression model is used to examine group differences when the outcome variables are binary, such as whether or not any inpatient services (or emergency room services) were used during the disease course. The multivariate logistic regression models estimate the effect of each covariate (predicting factor) on the likelihood of dichotomous outcome (e.g. any use of inpatient services) while other covariates are controlled for.

4.3.5 Data Analysis and Data Security

Source data and analysis data are stored on a secure data server with restricted access in the Sheps Center for Health Services Research at UNC. Data analyses are performed on a designated computer with password protection. Study results are communicated with caution to the Advisory Committee and others. No patient data are exchanged via email. All programming tasks pertaining to data management and statistical analyses are conducted with SAS (version 9.1.3, Cary NC).

An application was submitted to the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill. IRB approval was obtained prior to the data analysis for this study.

4.4 Study Methods for Aim 2 (budget impact study)

Budget impact analysis (BIA) is commonly used to address the financial consequences related to new health care technologies. In this study, it is extended to assess the financial impact of the change of use of new health care technologies. In the Aim 2 of this dissertation, a BIA is conducted to evaluate the financial impact of change in treatment strategy for Crohn's disease. More specifically, the BIA aims to evaluate payers' affordability of the increased use of biological therapies as CD treatment shifts from the conventional bottom-up to the aggressive top-down approach.

While cost-effectiveness analysis (CEA) evaluates both costs and outcomes of alternative technologies to determine their economic efficiency, BIA focuses on costs associated with alternative technologies. Since BIA is often used for budget planning and

forecasting by decision makers for health plans or third party payers, the BIA is conducted from the perspective of payers who manage and plan the budget of a specific healthcare program in a given time frame. According to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force principles of good research practice for BIA, the model does share many important methodological elements with CEA. Some key elements of the analytical framework for BIA are introduced in subsequent sections.

4.4.1 Decision Tree

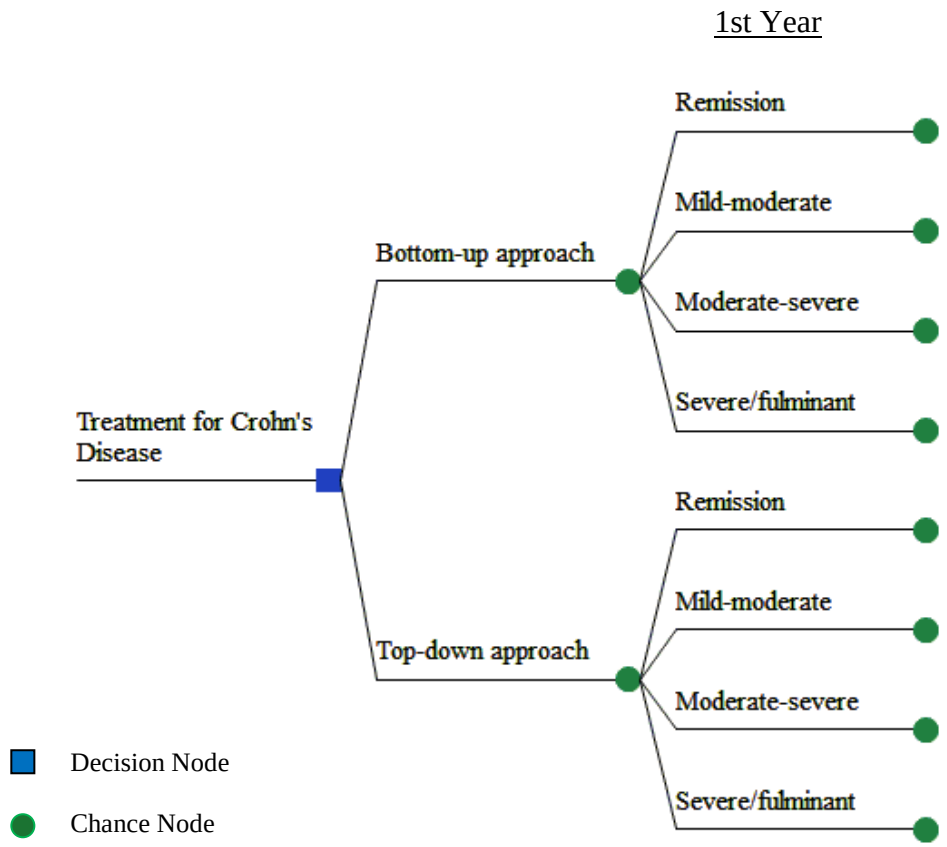
A decision tree model, as schematized in Figure 4.2, is designed as the analytical framework for the budget impact analysis in this dissertation. BIA compares prescription drug costs for CD patients use two treatment strategies, 'bottom-up' as base case scenario and 'top-down' as alternative scenario. Under the base case (reference) scenario, CD patients are compliant to existing treatment guidelines (2009 version) that follow the late adoption approach. All CD patients in the alternative (new) scenario are adapting to the early aggressive treatment approach that promotes the use of novel biological therapies in the early stage of disease. On the decision tree, the two scenarios are listed after the decision node (square).

In both treatment scenarios, CD patients are allocated into four exclusive outcome events according to disease severity, which includes remission, mild/moderate, moderate/severe, and severe/fulminant. Each outcome event, or a branch on the decision tree, is assigned a probability and associated with a certain amount of costs. The calculation for the probability and costs for each outcome (branch) is detailed in the following sections. On

the decision tree, possible outcomes are listed after the chance nodes (circle). Death is not included as an outcome for two reasons: 1) the death rate for CD patients is only slightly higher than the general population;[21] and 2) no death information for patients is available in the claims database to provide an estimation.

Prescription drug costs associated with each scenario (choice) is the summation of costs for each branch (outcome) multiplied by the assigned probability. The net difference in drug costs between two scenarios represents the financial impact on the annual budget for prescription drugs in a given year.

Figure 4.2 Decision Tree (schematic) for Budget Impact Analysis



4.4.2 Time Horizon

The BIA is conducted on an annual basis for the first, second and third year of CD to provide information on financial consequences of drug costs due to the treatment strategy change from the bottom-up to top-down approach. The costs and outcomes are evaluated and assigned annually.

4.4.3 Perspective

The perspective of the budget impact analysis is conducted primarily from that of pharmacy benefit management organizations (PBMOs), who are contracted by payers to manage prescription drug benefits. In the private sector of the US healthcare system, managed care organizations (MCOs) play a major role in providing healthcare to patients. Most MCOs use PBMOs to administer the pharmacy benefits. PBMOs negotiate drug price with manufacturers and purchase discounted drugs on behalf of MCOs. PBMOs also play a pivotal role in formulary design and provision of competitive benefit package to patients. When more and more specialty drugs (e.g., biological therapies) became available, PBMOs have evolved their function from the pharmacy counter to other sites, e.g., the infusion center. To cope with the complexity of specialty drugs, PBMOs usually develop specialty pharmacy programs to provide services to individual patients. Traditionally, all prescriptions filled at pharmacy counters are reimbursed by PBMOs under pharmacy benefits, and specialty drugs are administered by specialty pharmacy programs, but paid directly by payers under medical benefits.[67] Since the purpose of BIA is to predict the change in drug costs due to the treatment paradigm shift from the bottom-up to top-down treatment approach. We conduct

the BIA from a broader view of PBMOs to capture the drug costs for both conventional drugs, which are covered by pharmacy benefits, and biological therapies and costs associated with drug administration, which are covered by medical benefits.

4.4.4 Outcome Definition by Disease Severity

For an individual CD patient, the outcome of a particular treatment intervention can be measured in many different ways, such as treatment response, mucus healing, and quality of life. However, the outcome of a treatment for a large population cannot be measured simply due to the variety of treatment regimens, and the heterogeneity of treatment effects among CD patients. Usually, bedside clinical information is not readily accessible for researchers to conduct studies for outcome assessment. Without complications from individualized treatment and personal clinical experience, disease severity has been used by researchers to approximate treatment outcomes at the patient population level.[2] [68]

Disease severity is a key determinant in treatment planning for CD patients, although other factors, such as disease location, cost of therapy, patient compliance, and individual susceptibility to drug toxicity, can also be relevant in making therapeutic decisions. Therefore, patients with similar disease severities are presumably treated similarly. For example, it is recommended that patients with moderate/severe disease be treated with more than two doses of biological therapies. The change in disease severity can then represent the outcome of the recommended treatments. Given the heterogeneity of the disease, however, there is no 'gold standard' for the measurement of Crohn's disease severity. Crohn's Disease Activity Index (CDAI) is a disease-specific instrument used to quantify the symptoms of CD patients. According to the working definition of Crohn's disease activity in the practice

guidelines for adults published by the American College of Gastroenterology, Crohn's disease is classified into the following stages: a) remission (CDAI: <150); b) mild-moderate disease (CDAI: 150-300); c) moderate-severe disease (CDAI: 300-450); and d) severe/fulminant disease (CDAI: > 450).[11, 69] The CDAI-based classification system has been widely used in clinical trials for Crohn's disease.[8, 9] However, information on disease severity for individual patient is not readily available in claims databases for outcomes research.

Claim-based medical and pharmacological utilization information is used to approximate disease severity. Silverstein et al. used both type of therapy and patient response to therapy to define disease severity in their Markov model analysis from a population-based cohort.[2] Recently, Malone et al. modified the definitions for CD severity by incorporating both medical and pharmaceutical claims.[68] Classification of CD severity, as shown in Table 4.2, enables the definition of outcomes based on medical and pharmacological claims. In this dissertation, disease severity of Crohn's disease patients under either the bottom-up or top-down treatment approach is evaluated annually using pharmacy and medical claims. All claims within an observed year are checked with the criteria for severe/fulminant disease first, then with moderate-severe disease if not met severe disease, and so forth. This method has not been verified in an actual patient population. It is unknown how accurate the definition of disease severity is when compared with standard way in clinical practice. Due to the lack of direct medical information about patients' disease progression, the algorithm proposed by Malone et al. is used as a reasonable proxy for severity classification in this dissertation.

Table 4.2 Classification of Severity for Crohn's Disease

Severity Stage	Clinical Manifestations	Claims for Classification*
Severe/fulminant	persistent symptoms despite the introduction of conventional corticosteroids or biologic agents (infliximab, adalimumab, certolizumab pegol, or natalizumab) as outpatients, or individuals presenting with high fevers, persistent vomiting, evidence of intestinal obstruction, significant peritoneal signs such as involuntary guarding or rebound tenderness, cachexia, or evidence of an abscess	• Inpatient hospitalization admission with CD diagnosis; or • Diagnosis: obstruction, acute suppuration, perforation, refractory disease; or • Procedures: hyperalimentation; or • CD related procedures: surgical resection, stricturoplasty, colectormy ileostomy; or • Rx drugs: immunosuppressant, IV steroid
Moderate-severe	failed to respond to treatment for mild – moderate disease, or those with more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia	Does not meet criteria for severe/fulminant, and • Diagnosis: fistulas, abdominal mass, haemorrhage; or • Procedures: absess drainage; or • Rx drugs: biological agents (>2 doses), Prednisone, azathioprine, mercaptopurine, methotrexate; or • Symptoms: high fever, significant weight loss, abdominal pain/tenderness, anaemia
Mild-moderate	ambulatory and able to tolerate oral alimentation without manifestations of dehydration, systemic toxicity (high fevers, rigors, and prostration), abdominal tenderness, painful mass, intestinal obstruction, or >10 % weight loss	Does not meet criteria for severe/fulminant and Moderate-severe, and: • Rx drugs: mesalazine, sulfasalzine, metronidazole, ciprofloxaxin, budesonide, rifaximin
Remission	asymptomatic or without any symptomatic inflammatory sequelae	Does not meet criteria for severe/fulminant, Moderate-severe, and Mild-moderate.

CD: Crohn's disease

* Source: Malone, D.C. et al., A claims-cased Markov model for Crohn's disease. *Aliment Pharmacol. ther*. 2010; 32: 448-458

4.4.5 Prescription Drug Costs

Due to a lack of recent data regarding medical costs for CD patients with different disease severities, prescription drug costs for each disease severity classification for each year of disease are derived from the claims data from 2005 to 2009. In the decision tree for budget impact model, annual drug costs in the first three years of CD are the payoff values for each branch. Drug costs are not limited to the drugs prescribed to treat CD, but instead, costs for all-cause prescription drugs are included. Additionally, drug administrative costs (e.g., intravenous infusion costs) are also included for biological therapies that are administered intravenously or subcutaneously.

In MarketScan CCAE database, there are two types of prescription drug claims: a) traditional drug claims adjudicated with valid national drug codes (NDC), e.g., 00186070210 for Entocort (Budesonide); and b) specialty drug claims adjudicated with HCPCS J codes, e.g., J1745 for infliximab, J0135 for adalimumab, J2323 for natalizumab, and J0718 for certolizumab pegol. The following two financial variables, 'payment' and 'net payment', are used to calculate gross costs and net costs for prescription drugs. Gross drug costs are the sum of 'payment', and net drug costs are the sum of 'net payment' of all eligible claims in a given year. For patients who had no prescription claims, or had negative total amount of costs, their gross and net drug costs are set to zero. All payments incurred in each calendar year from 2005 to 2009 are adjusted with annual inflation rates for medical care to reflect the value expressed in 2010 US dollars ($).

Given the adequate sample size with around 3,000 eligible patients in both early and late biological user groups, prescription drug costs can be consistently estimated for patients in each disease severity classification.

4.4.6 Transition Probability

For budget impact analysis conducted in the first year of CD, the probabilities of each outcome under both scenarios are estimated by the proportion of biological therapy users in each category of disease severity in their first year of disease. For example, the probability of biological users having mild to moderate disease in the first year of disease will be 0.117 if there were 11.7% of biological users who experienced mild to moderate disease in their first year after diagnosis from 2005 to 2009 (see Table 4.3). In calculation of the probabilities for the first year CD patients, the proportions of biological users are based on distribution of all biological users, instead of early or late biological users. Sensitivity analyses are needed to address the difference in two biological user groups if their distribution on disease categories are significantly different.

Table 4.3 Distribution of Biological Therapy Users in the First Year of Crohn's Disease

	Remission	Mild-Moderate	Moderate-Severe	Severe/ Fulminant
Early users (N=3,082)	1,299 (42.2.%)	221 (7.2%)	946 (30.7%)	616 (20.0%)
Late users (N=2,986)	136 (4.6%)	487 (16.3%)	1,542 (51.6%)	821 (27.5%)
Biological users (N=6,068)	1,435 (23.6%)	708 (11.7%)	2,488 (41.0%)	1,437 (23.7%)

For BIA conducted in the second year of CD, the transition probabilities from the first year to the second year are calculated by the shift patterns of disease severity for CD patients from 2005 to 2009. The transition probability from initial disease severity in the first year of disease (e.g., mild to moderate) to present disease severity in the second year of disease (e.g., moderate to severe) is based on the proportion of patients who had mild-moderate disease in the first year, then have moderate and severe disease in the second year.

For example, if there were 104 CD patients among the bottom-up users with mild to moderate disease in the first year, and 44.2% of them (46 patients) had disease progressed to moderate and severe, then the transition probability from mild/moderate to moderate/severe is 0.442 (see Table 4.4). The transition probabilities for late and early users are calculated separately because of different effect from two treatment strategies.

Similarly, transition probabilities from the second year to the third year of disease are calculated based on the disease severity data in the second and third years of Crohn's disease.

Table 4.4 Transition Distribution of Biological Therapy Users in Three Years of Crohn's Disease

	n*	Remission	Mild-Moderate	Moderate-Severe	Severe/ Fulminant
Late biological users (n=2,986)					
1st year		===>	2nd year		
Remission	104	27 (26.0%)	14 (13.5%)	46 (44.2%)	17 (16.3%)
Mild-Moderate	368	63 (17.1%)	136 (37.0%)	106 (28.8%)	63 (17.1%)
Moderate-Severe	992	111 (11.2%)	76 (7.7%)	634 (63.9%)	171 (17.2%)
Severe/Fulminant	497	64 (12.9%)	61 (12.3%)	182 (36.6%)	190 (38.2%)
2nd year		===>	3rd year		
Remission	181	79 (43.6%)	34 (18.8%)	48 (26.5%)	20 (11.1%)
Mild-Moderate	156	23 (14.7%)	64 (41.0%)	44 (28.2%)	25 (16.1%)
Moderate-Severe	456	41 (9.0%)	37 (8.1%)	315 (69.1%)	63 (13.8%)
Severe/Fulminant	190	20 (10.5%)	17 (8.9%)	69 (36.3%)	84 (44.3%)
Early biological users (n=3,082)					
1st year		===>	2nd year		
Remission	816	563 (69.0%)	44 (5.4%)	123 (15.1%)	86 (10.5%)
Mild-Moderate	114	33 (28.9%)	44 (38.6%)	26 (22.8%)	11 (9.7%)
Moderate-Severe	543	136 (25.0%)	40 (7.4%)	298 (54.9%)	69 (12.7%)
Severe/Fulminant	391	116 (29.7%)	21 (5.4%)	82 (21.0%)	172 (43.9%)
2nd year		===>	3rd year		
Remission	480	298 (62.1%)	35 (7.3%)	108 (15.1%)	39 (10.5%)
Mild-Moderate	54	11 (20.4%)	16 (29.6%)	17 (31.5%)	10 (18.5%)
Moderate-Severe	209	35 (16.7%)	13 (6.2%)	128 (61.2%)	33 (15.9%)
Severe/Fulminant	152	41 (27.0%)	6 (3.9%)	38 (25.0%)	67 (44.1%)

* number of patients with full-year claims data in both starting and ending years of disease (e.g., 1st and 2nd, or 2nd and 3rd)

4.4.7 Model Assumptions

Several important assumptions are made for the budget impact analysis:

1. The prevalence of Crohn's disease will not increase or decrease significantly in the study time frame in the coming three years;
2. Annual inflation rates for medical care services is 4.0% in 2005, 4.4% in 2006, 3.8% in 2007, 3.3% in 2008, 3.6% in 2009 (The rate of increase in the Consumer Price Index for medical care service, Bureau of Labor Statistics).[70] All costs are expressed in 2010 US dollar ($).
3. No new drugs for the treatment of Crohn's disease will enter the drug market in the next three years.
4. No major pharmaceutical policies will be implemented so that payers do not need to change their current policy in the coming three years. Current clinical practice guidelines for CD treatment will remain the same with the exception that biological therapies are preferably used in the early stage of disease.

4.4.8 Base Case Analysis

In decision analysis, the base case is defined as 'status quo or keep safe and operating' without implementing alternate intervention. In the decision tree model for the current study, base case describes an average CD patient who uses biological therapy and other treatment following conventional bottom-up strategy in adopting biological therapy later in disease course. A patient in the base case has the same likelihood of having different disease severity

at the end of each year like other late biological adopters from 2005 to 2009, and incurs the same amount of prescription drug costs like others in previous years.

The alternative case refers to a scenario where new top-down treatment strategy is implemented in the clinical practice for CD patients. A patient in the alternative case follows early adoption treatment approach when biological therapies are included in their initial treatment. An alternative case patient has the same disease progression as other early biological users from 2005 to 2009, and uses the same amount of prescriptions as others.

Base case analysis compares the prescription drug costs between an alternative case patient with a base case patient, and determines the incremental cost of prescription drug costs of the alternative case by applying the estimated values of drug cost and probabilities for patients with different disease severity.

4.4.9 Sensitivity Analysis

In the base case analysis described above, there is considerable uncertainty with input parameters in the model due to a lack of or inaccurate information. Specifically, those uncertain parameters are: a) prescription drug costs for patients with different disease severity, and b) transition probabilities for patients with disease severity shifting from one year to its following year. Since no detailed cost information for CD patients with specific disease severity was available in the literature, we estimated the prescription drug costs and transition probabilities for patients classified in different disease severity according to their pharmaceutical and medical utilization of CD patients from 2005 to 2009. Point estimates of these parameters can not accurately represent their true values without taking into account the variation of healthcare utilization of an individual patient in the source data for this study.

Sensitivity analysis is a technique used to examine the uncertainties pertaining to the variation of prescription costs and transition probabilities. When presenting budget impact analysis results to decision makers, it is important to be specific about variation associated with all input parameters. Therefore, both base case analysis and sensitivity analysis are conducted in the budget impact model. While base case analysis demonstrates the incremental prescription drug costs due to the treatment strategy shift to early aggressive treatment, sensitivity analysis is performed to verify the robustness and variation of the estimation on budget impact.

Two types of sensitivity analyses are commonly applied in decision modeling: deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). In this dissertation, only PSA is chosen for decision analysis. DSA is often a one-way sensitivity analysis, which accounts for variation from a single input parameter under an assumption that the effect of each input variable is independent from others. However, most decision models involve multiple input parameters in combination so that their effects are not additive. The complexity of the budget impact model (e.g., multiple branches at each chance node) raises more concerns about the validity of DSA. On the other hand, PSA allows specifying variation of all input parameters simultaneously. In practice, a simple method to perform PSA is to use Monte Carlo simulations, which runs the model many iterations (e.g. 2000 trials) using randomly sampled values from distributions that are pre-specified for input parameters. The results from Monte Carlo simulations quantify the effect of variations on the uncertainty of the model. We use the 95% confidence interval of the simulation results to present the uncertainty estimated by PSA.

For PSA, distributions are selected to fit the input parameters for the budget impact analysis. Gamma distribution is recommended to fit prescription drug cost data, because cost data are highly skewed from normal distributions, and are constrained on the interval zero to infinity.[71] Dirichlet distribution is used to fit multinomial data for transition probabilities for each disease severity classification (remission, mild-moderate, moderate-severe, and severe/fulminant) at each chance node on the decision tree. Although beta distribution is often chosen to represent parameters with binomial data (constrained in the interval of 0 to 1), however, it is not applicable when the data are multinomial. As a conjugate prior of the parameters of multinomial distribution, Dirichlet distribution is frequently used to describe transition probabilities with more than two categories.[72] Details for parameter specifications for both gamma and Dirichlet distributions are provided in Table 4.5. All sensitivity analyses are conducted with TreeAge Pro 2011 (TreeAge Software Inc., Williamstown, MA).

Table 4.5 Parameters Specification in Sensitivity Analysis

Model Parameter	Base Case Value	Distribution Specifications
Prescription drug costs for patients classified to certain disease severity category (e.g. remission)	Mean of prescription drug costs of CD patients by treatment strategy (early or late adoption), disease severity, and time of disease (e.g., 1st year)	Gamma(κ, θ), where $\kappa = \bar{u}^2/s^2$, $\theta = s^2/\bar{u}$
Probabilities (in 1st year) or transition probabilities (in 2nd and 3rd years) of patients in certain disease severity category	Proportion of patients in a given disease severity, eg. a/(a+b+c+d) for disease remission where a, b, c and d stand for percentages of patients in each of four disease categories, respectively	Dirichlet (a; b; c; d), where a is percentage of patients with remission, b for mild-moderate disease, c for moderate-severe disease, and d for severe/fulminant disease

4.5 Study Methods for Aim 3 (cost study)

A cost analysis is conducted to more comprehensively evaluate the financial impact of the new treatment approach in CD treatment from payers' perspective. The cost analysis in the dissertation estimates the difference in costs incurred in all medical care services between two scenarios of treatment strategy, rather than the costs limited to prescription drugs in budget impact analysis. In addition to prescription drugs, other medical services, including hospitalization, emergency department visit, and outpatient visit, are reimbursed by payers, and are accounted for in total cost calculation. The algorithm for the identification of these different types of medical care services in the claims database is shown in Table 4.6. The total costs of all of these medical services can better represent the financial burden imposed to payers. A stable or modest decrease of total medical costs on payers because of the long-term impact of CD treatment paradigm change from bottom-up to top-down approach is ideal for payers to sustain the current benefit policy. On the contrary, a substantial increase of total medical costs can likely lead to a major formulary policy change to shift a larger portion of costs shared by patients. Therefore, the results from the cost analysis can provide evidence of long-term financial impact from the treatment strategy change. Although the cost analysis considers the costs from a larger scope of medical resource use, it shares the same analytic framework with the budget impact analysis in the previous section. The cost analysis also employs the same decision tree, and time horizon. The transition probabilities are identical, and sensitivity analyses are constructed similarly to budget impact analysis.

Table 4.6 Claims of Medical Services for Cost Analysis

Service Type	Description	Claims
Inpatient services	Claims associated with inpatient admissions, including hospital claims, physician claims, surgeon claims and claims from independent labs	All claims in Inpatient Services Table except the ones for emergency room services of MarketScan database
Outpatient services	Claims for services in a doctor's office, hospital outpatient facility, and other outpatient facilities	All claims in Outpatient Services Table except the ones for emergency room services
Emergency Room services	Claims for services in emergency room	All claims in both Inpatient and Outpatient Services Tables for emergency room facility. Selection criteria*: • STDPLAC=23; • STDPLAC=21,22,28 and (STDPROV=220 and STDSVC≠104 or STDSVC=77) • PROCGRP=110,111, and 114
Prescription Drugs	Claims for outpatient pharmaceutical use	All claims in Outpatient Pharmaceutical Claims Table

* Emergency room claims defined in MarketScan User Guide

4.5.1 Time horizon

Cost analysis is conducted in a three-year time frame from CD diagnosis to provide information of long-term financial consequences of health care costs because of the treatment paradigm change from late to early adoption treatment approach.

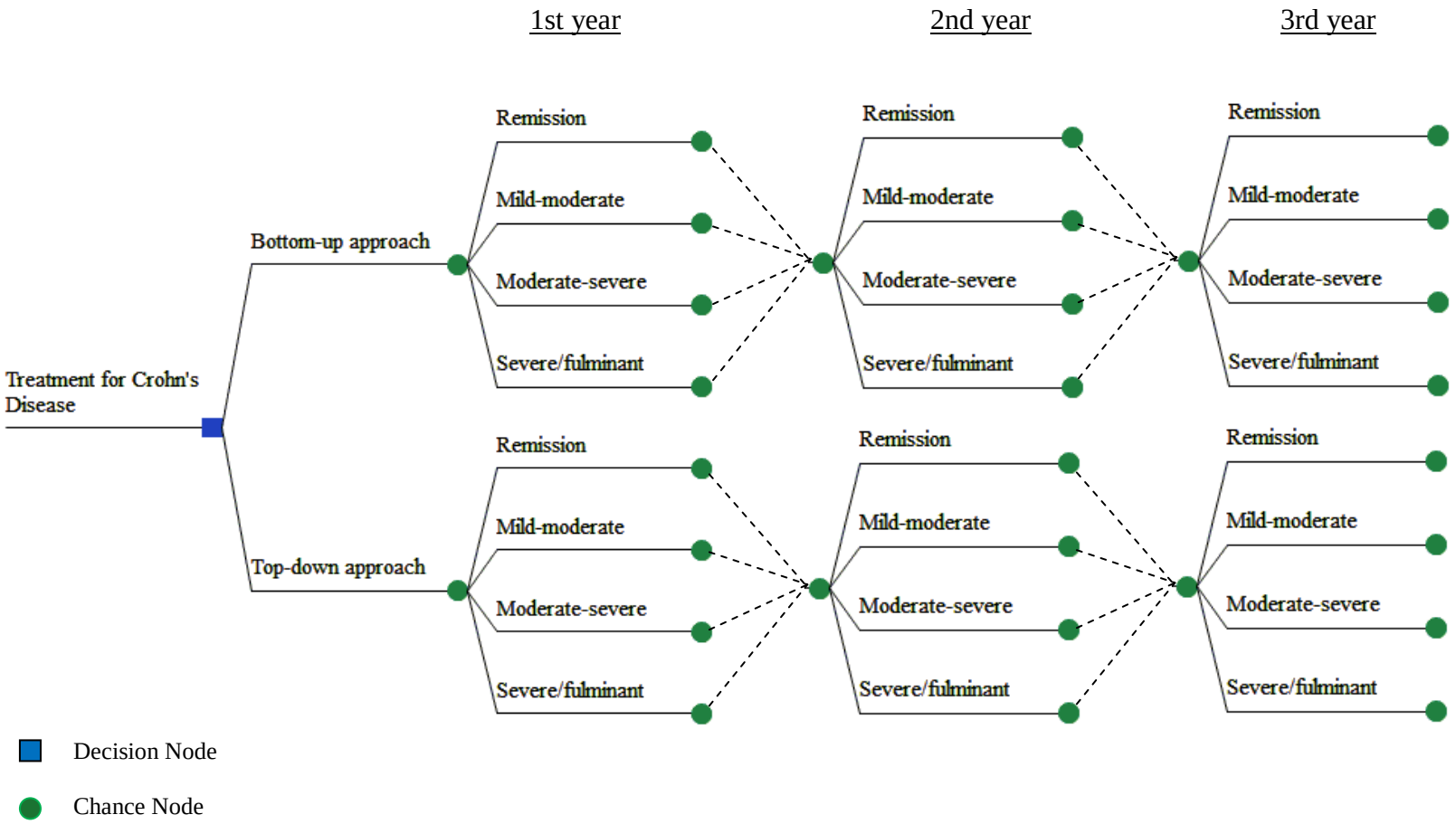
4.5.2 Decision Tree

A decision tree model in Figure 4.3 is constructed as the analytical framework for the cost analysis. The model compares health care costs (including prescription drug cost) of CD patients on an annual basis under two treatment strategies of disease management: bottom-up approach (the reference scenario) and top-down approach (the new scenario). In each year under either scenario, CD patients are allocated into four outcome levels according to disease severity: remission, mild/moderate, moderate/severe, and severe/fulminant. Each outcome (a branch on the decision tree) is assigned with a transition probability, and certain amount of healthcare costs. The calculation about the probability and costs for each outcome (branch) is elaborated in the sections below. The total costs of each scenario (choice) is the summation of the costs with each branch (outcome event) multiplying the corresponding transition probability. The difference of healthcare costs between two scenarios demonstrates the long-term financial impact of the treatment paradigm shift for CD management.

4.5.3 Healthcare Costs

Costs of a broader scope of healthcare services, including prescription drug, inpatient services, outpatient services and emergency room services, are taken into consideration in the cost analysis. Medical and pharmaceutical claims for different type of services in MarketScan claims database are classified by the algorithms in Table 4.6. The total cost on all four types of healthcare services is the primary economic outcome variable in the cost analysis. The analysis results based on the total healthcare cost can be used to demonstrate

Figure 4.3 Decision Tree for Cost Analysis



whether or not the treatment paradigm change is cost-saving. Meanwhile, costs on different types of healthcare services are considered as secondary economic outcomes. The results by service type (inpatient, outpatient, and prescription services) can be used to demonstrate the contribution to the saving of overall cost from each type of healthcare services.

On the decision tree, the cost associated with each branch (disease severity) is estimated by the average cost of CD patients with the same disease severity in previous years from 2005 to 2009. The estimation of total healthcare cost is obtained from the multivariate regression analysis in the cohort studies in Aim 1. For example, to predict the total cost of CD patients with mild disease in the first year of disease under the late adoption scenario, a multivariate linear regression analysis is performed by using the total cost of the same cohort of CD patients (mild disease under the late adoption approach) in the years from 2005 to 2009, and adjusted by the covariates (e.g. age, gender) in the previous sections.

All medical costs in previous years are adjusted by the annual inflation rate to reflect the present value, expressed in 2010 US dollar ($) as described in Section 4.4.7.

4.5.4 Transition Probability

The probability of each branch on the decision tree in the first year is based on the proportion of CD patients at the specific disease severity level from 2005 to 2009. For example, if 30% of biological users, under either bottom-up or top-down approach, were classified as mild disease, then the probability of mild disease in the first year is 0.3.

The transition probability of each branch on the decision tree in the second and third years is based on the average transition probabilities from the same severity levels in the previous year and following year. For example, the transition probability of a CD patient

under the bottom-up approach shifting from mild disease in the first year to moderate-severe disease in the second year is estimated by the proportion of CD patients under the bottom-up approach who shifted from mild disease in the first year to moderate disease in the second year of CD.

CHAPTER V:

HEALTHCARE UTILIZATION AND COSTS FOR COMMERCIALLY INSURED PATIENTS WITH CROHN'S DISEASE

Background: The treatment strategy for Crohn's disease (CD) is currently shifting from the conventional 'bottom-up' approach that reserves biological therapy as the last medical resort to a more aggressive 'top-down' approach that endorses early use of biological therapy. The impact of this shift in treatment on healthcare utilization and costs is unknown.

Objectives: This study sought to describe healthcare utilization and costs in patterns of treatment for Crohn's disease in a commercially insured population. Specifically, the purpose was to document healthcare utilization and costs for CD patients who adopted biological therapies early or late in their disease course.

Methods: The MarketScan Commercial Claims and Encounter database (2005-2009) was utilized as source data. CD patients who used biological therapies were grouped into early biological users if biological therapy was used as first-line treatment, and late biological users if other conventional medications were initially used in patients' course of treatment. We described the trend and pattern of healthcare services, including inpatient, outpatient, emergency room visits and prescription drug use. Total medical costs and costs of each individual service were summarized from the perspective of third-party payers. Multivariate

logistic regression and Generalized Estimating Equations were used to compare the utilization and costs of patients who underwent the two different treatment approaches.
Results: From 2005 to 2009, 18.2% of CD patients received at least one infusion or injection of biological therapy. Compared to late biological users, early biological users had 34% fewer inpatient visits and 17% fewer emergency room visits, and filled 50% fewer outpatient prescriptions. The annual costs of inpatient services for early adopters were also 32.2% lower than late biological users. However, prescription drug costs for early adopters were 26.4% higher. Overall, total medical costs for early adopters were 7.7% (95% CI: 3.0%-12.5%) more than later biological users. Factors contributing to these differences include patient age, employment status (e.g. large employer or not, full-time or part-time job status), and comorbid conditions.
Conclusion: Early aggressive treatment with biological therapies does not appear to be associated with significant changes in the overall costs for treating Crohn's disease.

5.1 Introduction

Crohn's disease (CD) affects approximately one half million Americans.[1] CD is characterized by diarrhea, abdominal pain, fatigue, fever, bowel obstruction and passage of blood and mucus, and associated with enormous financial burden to both patients and society.[2] The direct medical cost of CD to the U.S. health care system has been estimated at over $10 billion in 2006. [3] At present, Crohn’s disease is neither medically nor surgically curable.[11] Conventional medical therapies, including aminosalicylates (5-ASA), antibiotics, corticosteroids and immunomodulators, have a relatively low response rate and are

associated with many side effects. [29, 73] Biological therapies, mainly anti-tumor necrosis factors (a-TNF), have emerged as new therapeutic options based on their proven efficacy for CD in clinical trials, as well as success in treating other inflammatory conditions, such as rheumatoid arthritis and psoriasis.[32] However, these novel biological therapies cost five to ten times more than conventional drugs.[3, 74]

Historically, CD management guidelines recommended that patients begin treatment with conventional drugs, such as 5-ASA, oral steroids, and antibiotics, because of their better toxicity and safety profile than immunosuppressive medicines.[69] Under these guidelines, biological therapies are generally reserved as the last medical resort. This so-called 'bottom-up' treatment strategy has been traditionally accepted in clinical practice, and relies on the initial use of inexpensive conventional treatments with more expensive biological therapies reserved for patients who are refractory or intolerant to conventional drugs . Recently, however, a more aggressive treatment approach, referred to here as the 'top-down' approach, has received considerable attention because it promotes treatment with expensive biological therapy early in the course of treatment before conventional drugs are ever attempted. This top-down treatment approach is now thought to change the natural course of disease progression by reducing complications of stricturing and fistulization, which often require surgery.[37] Indeed, two newly completed clinical trials suggest that the top-down regimen results in more rapid and frequent remission.[12, 13]

Four biological therapies have been approved by the FDA (i.e. Infliximab in 1998, Adalimumab in 2007, Natalizumab and Certolizumab pegol in 2008) to treat CD. These new therapeutic options, combined with evidence for their effectiveness early in the course of CD, have likely shifted treatment patterns for CD. However, there is limited information about

utilization patterns and costs of various healthcare services for CD patients over time. Feagan et al. examined the costs of different medical services in a claims database (1994-1995), and reported that the annual cost was $12,417 for a CD patient.[5] Gibson et al. found that annual total medical cost increased to $18,962, based on claims data from 1999 to 2005.[42] More recently, Kane et al. and Kappelman et al. compared healthcare utilization and costs between biological and non-biological users, and found that biological users incurred substantially higher prescription drug costs.[6, 44] However, findings from both studies were based on data prior to 2006, and do not capture trends in utilization resulting from the approval of newer biological therapies.

For the current study, a large administrative database containing medical and pharmacy claims was analyzed to describe the use of biological therapies and direct medical costs to payers among CD patients from 2005 to 2009. The objectives of this study were to: a) describe recent annual trends in the prevalence of biological therapy use among patients with CD; and b) summarize the utilization and costs of inpatient, outpatient, and emergency room services, as well as prescription drugs for CD patients who initiated biological therapy using different treatment strategy. The results of this study will provide third-party payers, providers, and CD patients with important financial information regarding recent trends in the utilization and costs of healthcare services for Crohn's disease, and the potential influence of different strategies for CD treatment on these variables. Study results can also be used to predict future use and costs of biological therapies to help facilitate more extensive economic evaluations on these biological therapies under different treatment approaches.

5.2 Methods

Data Source

The data source for this study was the MarketScan Commercial Claims and Encounter (CCAE) database (Thomson Reuters, Ann Arbor, Michigan) comprised of patient data from January 1, 2005 to December 31, 2009. This database captured person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services from approximately 100 payers including large employers and health plans. From 2005 to 2009, there were data from nearly 73 million insured individuals in the MarketScan CCAE database.

Patient Selection

The process of patient selection was illustrated in Figure 5.1. The source population for the study was comprised of individuals from a MarketScan CCAE database meeting the following inclusion criteria: a) a diagnosis of Crohn's disease (ICD-9 code: 555.x); b) between 18 and 64 (inclusive) years of age at initial diagnosis; c) a minimum of one year of continuous enrollment after the diagnosis of Crohn's disease; d) who were enrolled in managed care organizations; and e) who were incident CD patients with no CD history. We restricted the sample to incident users following a new user design to avoid selection bias due to under-ascertainment of early events and to control for risk factors that may be altered by the intervention.[75] Therefore, patients were required to have no CD diagnostic claims or prescription treatment for CD for a minimum of six months before the index date of the first CD treatment. To eliminate patients with diagnostic claims related to symptoms of CD who did not have a confirmed diagnosis of CD, we required patients to have both a diagnosis

claim for CD and at least one prescription for medications used to treat CD, including non-biological drugs (mesalamine, sulfasalazine, metronidazole, ciprofloxacin, rifaximin, azathioprine, methotrexate, mercaptopurine, budesonide (Entocort only), cyclosporine, and tacrolimus), and biological agents (adalimumab, infliximab, natalizumab, and certolizumab pegol). Oral steroids (i.e. prednisone, prednisolone) were not included in the patient selection algorithm due to their relatively low specificity.[6] We further restricted our sample to exclude patients diagnosed with the following conditions since these conditions can be treated with the same biological therapies used to treat Crohn's disease: a) ulcerative colitis (ICD-9 codes: 556.xx inclusive); b) rheumatoid arthritis (ICD-9 codes: 714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 714.4, 714.81, 714.89, 714.9); c) ankylosing spondylitis (ICD-9 code: 720.0); d) psoriatic arthritis (ICD-9 code: 696.0); e) plaque psoriasis (ICD-9 code: 696.1); and f) juvenile idiopathic arthritis (ICD-9 code: 714.3). Among nearly 73 million individuals in the MarketScan CCAE database, 33,428 patients met eligibility criteria for the study (see Figure 5.1).

The study cohort was grouped into either biological users or non-biological users. Biological users were defined as patients who used any biological therapy during the disease course from the initial diagnosis to the end of enrollment or the last day of follow-up on December 31, 2009. There were 6,068 patients who used at least one dose of biological therapy.

Biological users were further classified into either early or late biological users according to their initial medical treatment. If one of the biological therapies was included in the patients' initial medical treatments, those patients were categorized as early biological users. Late biological users were those patients who used biological therapies after

attempting other conventional drugs. Among all biological users, 3,082 of them included biologics in their initial CD treatment, and 2,986 patients used biologics later.

Outcome Variable Definitions

Outcomes for this study include a series of variables that describe the utilization and costs of healthcare services used by CD patients in different healthcare service areas, including inpatient, outpatient, and emergency room as well as prescription drugs. Utilization and costs were examined for all causes, regardless of whether the service was targeted at CD, because diagnosis codes associated with claims may not reflect the exact medical cause.

Binary variables were used to categorize patients as having received either inpatient or emergency room services during the entire disease course from the date of diagnosis to the end of enrollment. Five continuous numeric variables were defined to quantitatively represent the annual utilization of healthcare services, including the number of inpatient, outpatient, and emergency room visits, number of prescriptions filled and length of inpatient stays (number of days). For patients enrolled in more than one year, the utilization variables were annualized by first calculating the monthly rate (the amount of utilization divided by duration of disease in months), then multiplying by twelve.

Healthcare costs consisted of payments from the following three parties: a) out-of-pocket payments made by patients (i.e. deductibles, copayments, and coinsurance); b) payments made by third-pay payers (i.e. net payment); and c) payment coordination of benefits (i.e. COB, or other savings). The total payment from all three parties represents the direct medical cost to society, where net payment denotes the costs incurred by payers. Both total payment and net payment were summarized according to patient groups. In addition to

the sum of costs for all health care services, four separate variables were defined to depict costs for inpatient, outpatient, emergency room services, and prescription drugs. For each patient, cost variables consisted of the average costs for all healthcare services or individual healthcare service across all enrolled years. All costs were adjusted to the value of the U.S. dollar in 2010 using the medical consumer price index.

Independent Variables

Healthcare utilization and costs for patients with chronic illness can be explained by a wide range of internal factors (e.g., patient characteristics) and external variables (e.g., provider specialty).[76] We characterized patients on the basis of Andersen's model for healthcare utilization, which posits that healthcare utilization is dependent upon predisposing factors (the predisposition of the patient to use healthcare services), enabling factors (patient's ability secure services), and need factors (disease severity).[60] In the current study, predisposing variables included patient age at initial diagnosis of Crohn's disease, gender and calendar year of disease diagnosis (i.e., 2005, 2006, 2007, 2008, and 2009). Enabling factors included health plan type (e.g., preferred provider organizations (PPO) or others), employment status (e.g., active full time employee or others), relationship with employee (e.g.,employee or spouse/dependents), geographic region (e.g., northeast, north central, south, or west), urban residence (e.g., metropolican statistical area or not), and employer size (e.g., large employers or smaller firms under health plans). Need factors included provider specialty at initial diagnosis (e.g., gastroenterologist or not), comorbid conditions (e.g., Charlson comorbid index score based on utilization information in the six-

month 'washout' period prior to the initial diagnosis),[77] and prescription use in the washout period (e.g., number of prescriptions filled in the past six months prior to the initial diagnoses).

Statistical Analysis

Descriptive statistics for both outcomes and independent variables were conducted on all eligible CD patients and subgroups, including biological and non-biological users. Among biological users, characteristics and outcomes of early biological users were compared with late users by applying two-way ANOVA tests for numerical variables (e.g., age) and the Cochran-Mantel-Haenszel test for categorical variables (e.g., health plan type). Descriptive statistics for these variables in each patient cohort are provided.

A logistic regression model was used to estimate the effect of patient characteristics in predicting the preference in treatment approach for patients when biological therapies were included in the treatment algorithm. In this model, the response variable was coded to '1' for patients who used the top-down treatment, and coded to '0' for patients following the bottom-up strategy. Two logistic regression models were used to demonstrate differences in the likelihood of using both inpatient services and emergency room services between top-down and bottom-up biological users, controlling for patient characteristics.

Generalized estimating equation (GEE) regression was used to estimate the differences in utilization and cost variables between top-down and bottom-up biological users, controlling for patient characteristics as covariates. The GEE models are specified as follows in a general form where the response variable can be one of the utilization outcome

variables, such as average number of inpatient visit per year or average net cost of prescription drugs per year.

$$Y = \beta_0 + \beta_1 X_{Early} + \beta_i X_{demog} + \beta_j X_{health} + \beta_k X_{ins} + \beta_l X_{emp} + \beta_m X_{provider} + \beta_n X_{year} + \varepsilon$$

where, Y represents an outcome variable, X_{Early} is the key independent variable that indicates whether a patient is an early biological user (coded to '1'), or a late biological user (coded to '0'). Covariates used in the model include: a) X_{demog} represents a group of demographic variables, including age, gender, urban residency, and region; b) X_{health} represents health status, indicated by the Charlson Comorbidity Index (*CCI*) and total number of prescriptions in the washout period; c) X_{ins} denotes the type of benefit plan (PPO, POS, FFS, and other); d) X_{emp} represents employment status (e.g., full-time or not), relationship to employee (e.g., employee or spouse/dependent) and employer size (e.g., large firm vs. small firm); e) $X_{provider}$ represents characteristics of the provider (e.g., specialty); and f) X_{year} represents a given calendar year from 2005 to 2009.

All analyses were performed with SAS, version 9.1.3 (SAS® Cary, NC). The study was approved by the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill.

5.3 Results

Study Patients

Among 33,428 eligible Crohn's disease patients whose data comprised the MarketScan database from 2005 to 2009, 18.2% (n=6,068) received at least one infusion or injection of

any biological therapy, including Infliximab, Adalimumab, Natalizumab, or Certolizumab pegol. In each year from 2005 to 2009, the percentage of biological users among prevalent CD patients persistently increased from 7.0% in 2005 to 15.4% in 2008, and 18.% in 2009 (not including CD patients who were diagnosed after January 1, 2009). The notable growth in 2008 and 2009 is likely related to the FDA's approval for new biological therapies (see Appendix Tables 5.1, 5.2 and Figure 5.2).

Compared to non-biological users, biological users were significantly younger (biological users: 37.9 vs. non-biological users: 43.1, $p< 0.001$), more likely employed by smaller firms than large employers (56.7% vs. 41.5%, $p<0.001$), had fewer comorbid conditions measured by the Charlson comorbidity index (0.05 vs. 0.18, $p<0.001$), and used fewer prescriptions in the past six months prior to their diagnosis of Crohn's disease (1.61 vs. 5.32, $p<0.001$) (see Table 5.1). Logistic regression confirmed that these patient characteristics were significant predictors for biological therapy use (see Appendix Table 5.5).

Among 6,068 biological therapy users, 50.8% (n=3,082) of patients used biological therapies as their initial medical treatment, and 49.2% (n=2,986) of patients used other non-biological therapies as first-line medical treatment. Compared to the late biological users, early adopters had similar characteristics, for example, age at diagnosis (38.0 vs. 37.7), proportion of females (53.1% vs. 55.0%), percentage of urban residents (86.7% vs. 85.4%), the likelihood of being diagnosed by a gastroenterologist (28.2% vs. 32.8%), and comorbid conditions measured by the Charlson Comorbidity index (0.03 vs. 0.06). These two groups of patients were also categorically different in many aspects. For example, early biological users were more likely enrolled in health plans offered by smaller firms than those covered large employers (71.7% vs. 41.2%, odds ratio=2.10, CI: 1.69-2.60), and less likely employed as

active full-time employees (27.0% vs. 55.1%, OR=0.73, CI: 0.59-0.91). In addition, early biological users consumed fewer prescriptions in the past six months prior to their CD diagnosis (0.55 vs. 2.71, OR=0.83, CI: 0.80-0.85) (see Table 5.1 and Appendix Table 5.4).

Healthcare Utilization

The descriptive statistical summary showed differences between the early and late biological users in inpatient visits, length of inpatient stays, outpatient visits, emergency room visits, and number of prescription drugs (see Table 5.2). Generalized estimating equations (GEE) models estimated statistically significant differences in healthcare utilization between these two biological user groups. When compared to the late biological users, early users had 34% (95% confidence interval: 25%-43%) fewer inpatient visits per year (0.32 vs. 0.47), had 28% (CI: 24%-32%) fewer days of inpatient stays per year (1.61 vs. 2.27), had 17% (CI: 5%-28%) fewer emergency room visits per year (0.85 vs. 0.97), and 50% (CI: 45%-54%) fewer prescriptions filled per year (16.94 vs. 31.72). The difference in number of outpatient visits per year between early and late biological users was not statistically significant (see Appendix Table 5.6 and Appendix Figure 5.1).

Healthcare Costs

Total costs to the healthcare system and net costs to payers for all services and service areas are summarized in Table 5.2. The annual total costs of all healthcare services were $32,820 (standard deviation: $28,788) for biological users, and 92% of the total costs, or

$30,213 per year (SD: $27,538) were paid by third-party payers. Among the total net cost, 51.0% was attributable to prescription drug costs, equivalent to $15,410 per year (SD: $12,672).

Comparisons of healthcare costs were also made between the early and late biological users. The total net costs for early adopters was $30,785 per year (SD: $29,137), which is 7.7% (95% confidence interval: 3.0%-12.5%) higher than late biological users, whose costs were $29,623 per year (SD: $25,775). When comparing net costs for each healthcare service area, the results showed that early biological users incurred 26.4% higher costs for prescription drugs ($17,209 vs. $13,554, CI: 22.1%-30.7%), but had 32.2% lower costs for inpatient services ($4,942 vs. $6,934, CI: 15.6%-48.9). Differences in the annual net costs of outpatient and emergency room services between early and late users were not statistically significant. GEE regression results showed that age at diagnosis, provider specialty of initial diagnosis, employment status, and comorbid conditions were the factors that contributed most to the total net cost difference between the two biological user groups (see Table 5.3, Figure 5.3 and Appendix Table 5.7).

5.4 Discussion

Our results suggest that the use of biological therapy for Crohn's disease has increased significantly over the past five years from 7.0% in 2005 to 18.4% in 2009. Despite the economic recession from December 2007 to June 2009, the annual increase of biological therapy use is steady because of the market diffusion of individual biological therapies, and the expansion of the biological drug class with three biological therapies approved by the

FDA in 2007 and 2008. When more biological therapies are under investigation in clinical trials [32] and the US economy is continuously recovering, it is projected that more than 20% of CD patients would be receiving biological therapies in 2010. The increasing use of biological therapies can result in substantial financial pressure on payers, particularly managed care organizations, because of the high cost of these drugs. While managed care organizations have made an effort toward cost containment, [78] the expansion of biological therapies as treatment for CD patients could increase budgetary pressures to control CD healthcare spending. In response, aggressive measures may be taken by managed care organizations to contain costs, which would reduce access to advanced treatment that may benefit patients. In fact, more and more insurance plans adopted co-insurance, instead of flat-fee co-payment, as the cost-sharing method of choice for biological agents for patients with rheumatoid arthritis.[79]

Our results suggest that the use of biological treatment for Crohn's disease differs according to several patient characteristics and healthcare system factors. Although the demographic characteristics differentiate who receives biological treatment overall, they explain less clearly how early or aggressively biological therapy is initiated among biological users. Biological users were, on average, five years younger than non-biological users. However, the average age of early biological users was not significantly different from late biological users. This suggests that there is a lack of evidence to support the contention that biological users are different in age at onset of CD, thus, biological users can be considered as a homogeneous group. This can simplify cost-effectiveness modeling without stratifying patients into different age groups. Other patients' demographic characteristics, including gender, geographic region, urban residence, and year of initial diagnosis, did not appear to be

notably different between two biological user groups. However, we noticed that they were different in several important aspects. Early biological users had much lower comorbidity scores, and filled smaller number of prescriptions during six months before the diagnosis of Crohn's disease. These were the indicators that early biological users may have better general health condition than late users.

Another difference was patient employment status, which showed that early biological users were less likely to be full-time employees and less likely to be employed by large employers. It is believed that health benefits provided by larger employers are more generous than those provided by small firms.[80] Counter-intuitively, patients with less generous healthcare coverage are more likely to use advanced treatments, which may be related to awareness of expiration of their employment based insurance. Biological therapies are associated with high costs, average wholesale prices (AWP) are $754.50 for infliximab 100 mg (Remicade®), $865.58 for adalimumab 40 mg (Humira®) and $822.30 for certolizumab pegol 200 mg (Cimzia®). It is natural for patients to be prone to use more expensive treatment options when they have health insurance coverage, but are concerned about the continuity of their employment and/or healthcare benefit plans while working at small firms. Therefore, patients from small employers use biological therapies earlier in the disease course when they have milder disease. Given that specific information about the generosity of health plans was not available in the source dataset, further study is needed to confirm whether or not employers' size is a valid indicator of a health plan's generosity of coverage.

It was interesting to note that early biological users were less likely to be full-time employees than late biological users. Employment status (i.e., active full-time or part-time

job status) and healthcare benefits are highly associated with firm size.[81] Large firms offer more full-time positions, and provide health insurance to employees with better coverage.[82] It may be reasonable to assume that employment status is associated with the health status of patients. Patients with severely active CD that experience frequent flare-ups may have greater disability preventing them from working at full-time jobs. Due to a lack of information in our source data about employment status and disability conditions, it is unknown about their effect in predicting healthcare utilization and costs.

The total medical costs in this analysis are consistent with findings from previous studies. The average total cost of medical services for all CD patients was $18,880 (standard deviation: $32,228), which is higher than results reported by Kappelman and colleagues ($10,952 in 2004).[6] The increase in total medical costs reflect the trend that more Crohn's disease patients are using biological therapies. The average total cost for biological users was $32,820 (standard deviation: $28,788), which is lower than Kane and Sandborn's calculation based on the planned dose schedule. This difference may be attributable to non-compliance among some patients in our source data.

The most striking finding in the cost analysis when comparing the two biological user groups is that the overall medical costs paid by third-party payers for early biological users ($30,785) were only 3.9% higher than those paid for late users ($29,623). These results suggest to payers that the new treatment strategy change for CD patients toward early aggressive biological therapy use had not incurred a dramatic surge in overall payments. It was also found that total medical costs, including the net payments by payers, out-of-pocket payments by patients, and coordination of benefits (COB) and other savings, were $33,263 for early and $32,362 for late biological users. The differences between total medical costs

and net payment by payers for early and late users were $2,478 and $2,739, respectively. This indicates that out-of-pocket costs of prescription drugs for CD patients is nearly the same, regardless of the treatment approach. Furthermore, our results demonstrate that the cost pattern shifted from inpatient services to prescription drugs when utilization and costs were analyzed by healthcare service area. Compared to the late biological users, early users incurred higher costs for prescription drugs, and lower costs for inpatient services, when compared to costs for outpatient and emergency room services. As biological therapy use becomes more common and is implemented earlier in the course of CD treatment, managed care organizations are concerned about the expense of these treatments. Further research is needed to demonstrate the short-term budgetary impact from increased drug costs due to the treatment strategy shift toward more aggressive biological therapies, and the long-term cost-effectiveness of this aggressive treatment approach for CD patients.

We used a dichotomized approach and classified biological therapy users into early and late user groups according to whether or not biological therapies were used within three days after their first CD treatment. We used the general consensus about top-down and bottom-up strategy in defining patient cohorts since there is no unified definition for both top-down and bottom-up therapy from clinical perspective. In practice, medical therapy for CD patients is often individualized according to disease severity, location, and health condition. Meanwhile, the claims data used in this study do not contain comprehensive medical and clinical information. Although top-down treatment suggests patients to start with biological therapy immediately after their diagnosis, some clinicians would include patients who used biological therapies right after steroids. We examined patients who used steroids as the first medical therapy, and found their utilization and healthcare costs were homogenous

to other late biological users. Therefore, we included steroid users in the late user group. The bottom-up strategy requires patients to start with less potent therapies. We found the order of therapies was diversified, and only a small portion of patients strictly followed the disease management guidelines. Given the complexity of treatment pattern for CD patients, we consider early users using top-down and late users using bottom-up treatment strategy, respectively.

The results of this study must be interpreted in light of the study's limitations. First, the study results were based on a well-defined patient population with strict selection criteria. Eligible patients were enrollees of managed care organizations in a large commercial claims database. Patient groups were required to meet age criteria, continuous enrollment status, and were newly diagnosed with a clean six-month washout period. Although these patients can represent a large portion of the US population, especially in people under 65, they may be categorically different from patients insured by other government programs, such as Medicaid and Medicare. External validity needs to be assessed further before extrapolating findings from this study to other patient population.

Second, patient group classification in this study was largely based on pharmacy and medical claims instead of medical records. Although claims data contains comprehensive healthcare service utilization information, medical information within claims data may lack accuracy. For example, the diagnosis code related to many medical procedures can not confirm whether a visit truly resulted in a diagnosis or served as a means of ruling out other conditions. In the study methodology, some measures were taken to remedy the issues concerning the accuracy of the diagnosis by requiring all CD patients to have filled at least one prescription for medication used to treat Crohn’s disease. Furthermore, claims data only

captures pharmacy or medical utilization where insurance claims were filed. Free or self-paid drug samples/procedures were not included in the claims database, which could lead to misclassification. In particular, some early biological users might be misclassified if they received medications that were not in the claims data prior to FDA approval of biological therapies. Inaccurate and incomplete claims data could threaten the internal validity of this study.

5.5 Summary

Biological therapies were increasingly used among Crohn's disease patients from 2005 to 2009. From comparisons of healthcare utilization between early and late biological users, we found that both user groups utilized a similar amount of outpatient services, but early users utilized less inpatient and emergency room services, and filled a fewer number of prescriptions. Compared to the late users, early users incurred more costs for prescription drugs, but fewer expenses for both inpatient and emergency room services. Despite differences in costs for each service area, the total healthcare costs paid by third-party payers were not categorically different between two biological user groups. This indicates that increased drug costs for top-down users could be offset by the reduction in inpatient and emergency room services. These results suggest that early aggressive treatment of CD with biological therapy may not incur significant additional expense to health insurers. Further studies are needed to investigate the budgetary impact and cost effectiveness of incorporating biological treatments early into CD treatment regimens.

Figure 5.1 Study Sample Selection

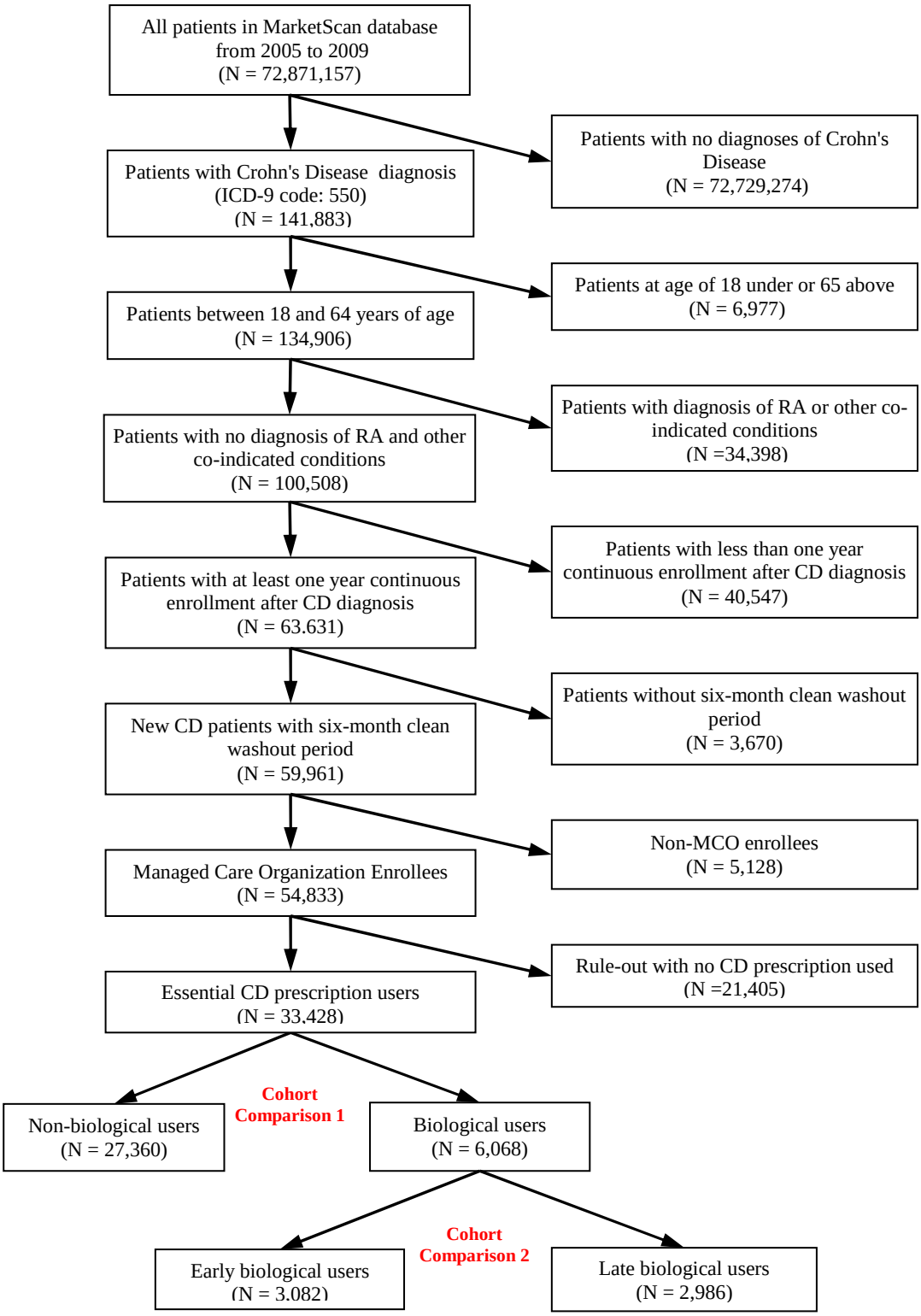


Table 5.1 Characteristics of Crohn's Disease Patients

Characteristics	Non-biological Users	Biological Users	P-value*	Early Biological Users	Late Biological Users	P-value*
Total number of patients	27,360	6,068		3,082	2,986	
Year of disease diagnosis,%			<0.001			<0.001
2005	5,863 (21.4%)	920 (15.2%)		290 (9.4%)	630 (21.1%)	
2006	6,640 (24.3%)	1,689 (27.8%)		1,038 (33.7%)	651 (21.8%)	
2007	4,966 (18.2%)	916 (15.1%)		405 (13.1%)	511 (17.1%)	
2008	9,471 (34.6%)	2,480 (40.9%)		1,321 (42.9%)	1,159 (38.8%)	
2009	420 (1.5%)	63 (1.0%)		28 (0.9%)	35 (1.2%)	
Age at diagnosis, mean (SD)	43.1 (12.5)	37.9 (12.2)	<0.001	38.0 (12.3)	37.7 (12.2)	0.364
Age at 40 years or above, %	16,826 (61.5%)	2,609 (43.0%)	<0.001	1,327 (43.1%)	1,282 (42.9%)	0.923
Female, %	16,080 (58.8%)	3,281 (54.1%)	<0.001	1,638 (53.1%)	1,643 (55.0%)	0.143
Diagnosed by GI specialist, %	7,667 (28.0%)	1,846 (30.4%)	<0.001	868 (28.2%)	978 (32.8%)	<0.001
Region,%			<0.001			<0.001
Northeast	3,591 (13.1%)	733 (12.1%)		365 (11.8%)	368 (12.3%)	
North Central	8,567 (31.3%)	2,004 (33.0%)		1,102 (35.8%)	902 (30.2%)	
South	11,502 (42.0%)	2,675 (44.1%)		1,336 (43.3%)	1,339 (44.8%)	
West, or unknown	3,700 (13.5%)	656 (10.8%)		279 (9.0%)	377 (12.6%)	
MSA, %	23,164 (84.7%)	5,221 (86.0%)	0.007	2,671 (86.7%)	2,550 (85.4%)	0.155
Large employers, %	25,999 (58.5%)	2,628 (43.3%)	<0.001	872 (28.3%)	1,756 (58.8%)	<0.001
PPO, %	19.261 (70.4%)	4,487 (73.9%)	<0.001	2,460 (79.8%)	2.027 (67.9%)	<0.001
Fulltime employee, %	14,187 (51.9%)	2,479 (40.9%)	<0.001	833 (27.0%)	1,646 (55.1%)	<0.001
Non-dependent employee, %	17,351 (63.4%)	3,824 (63.0%)	0.560	1,946 (63.1%)	1,878 (62.9%)	0.842
CCI, mean (SD)	0.18 (0.70)	0.05 (0.28)	<0.001	0.03 (0.22)	0.06 (0.33)	<0.001
Rx prior to diagnosis, mean (SD)	5.32 (9.14)	1.61 (4.57)	<0.001	0.55 (1.87)	2.71 (6.05)	<0.001

* P values were obtained from a Cochran-Mantel-Haenszel test for categorical variables (eg. year of diagnosis), and from a two-way ANOVA test for numerical variables (eg. age) while comparing the characteristics between early and late biological users.

SD: standard deviation; MSA: metropolican statistical area; GI: gastroenterologist; PPO: preferred provider organization; CCI: Charlson comorbidity index

Table 5.2 Summary of Healthcare Utilization and Costs

Outcomes	All Eligible CD Patients	Non-biological Users	Biological Users	Early Biological Users	Late Biological Users
Total number of patients	33,428	27,360	6,068	3,082	2,986
Patients with any inpatient visit, %	11,724 (35.1%)	9,239 (33.8%)	2,485 (41.0%)	1,041 (33.8%)	1,444 (48.4%)
Inpatient visits per year	0.32 (0.76)	0.30 (0.75)	0.39 (0.80)	0.32 (0.78)	0.47 (0.82)
Days of inpatient stays per year	1.55 (6.02)	1.46 (6.10)	1.93 (5.62)	1.61 (5.93)	2.27 (5.26)
Total payment of inpatient services	$5,361 (21,251)	$5,150 (21,661)	$6,313 (19,267)	$5,248 (20,170)	$7,412 (18,226)
Net payment of inpatient services	$5,029 (20,632)	$4,831 (21,108)	$5,922 (18,308)	$4,942 (19,304)	$6,934 (17,164)
Patients with any outpatient visit, %	33,235 (99.4%)	27,195 (99.4%)	6,040 (99.5%)	3,080 (99.9%)	2,960 (99.1%)
Outpatient visits per year	18.16 (16.38)	17.44 (16.22)	21.44 (16.20)	21.47 (16.71)	21.42 (15.66)
Total payment of outpatient services	$7,451 (13,880)	$7,118 (14,429)	$8,951 (10,947)	$8,587 (10,866)	$9,327 (11,019)
Net payment of outpatient services	$6,543 (13,334)	$6,160 (13,765)	$8,269 (11,020)	$8,083 (11,223)	$8,460 (10,804)
Patients with any ER visit, %	17,674 (52.9%)	14,171 (51.8%)	3,503 (57.7%)	1,658 (53.8%)	1,845 (61.8%)
ER visits per year	0.78 (2.18)	0.75 (2.23)	0.91 (1.92)	0.85 (1.83)	0.97 (2.00)
Total payment of ER services	$621 (2,446)	$601 (2,499)	$709 (2,190)	$646 (2,324)	$774 (2,040)
Net payment of ER services	$540 (2,999)	$523 (2,385)	$613 (1,859)	$551 (1,874)	$676 (1,842)
Number of Rx per year	24.77 (23.43)	24.89 (23.57)	24.21 (22.78)	16.94 (18.35)	31.72 (24.41)
Total payment of Rx services	$5,447 (8,809)	$2,919 (4,521)	$16,848 (13,288)	$18,782 (14,953)	$14,850 (10,964)
Net payment of Rx services	$4,766 (8,288)	$2,406 (4,199)	$15,410 (12,672)	$17,209 (14,191)	$13,554 (10,568)
Total payment of all services	$18,880 (32,228)	$15,788 (32,133)	$32,820 (28,788)	$33,263 (30,329)	$32,362 (27,104)
Net payment of all services	$16,878 (31,010)	$13,921 (30,960)	$30,213 (27,538)	$30,785 (29,137)	$29,623 (25,775)

ER: emergency room, Rx: prescription
All costs are adjusted to 2010 US dollar ($) with annual CPI inflation rate of medical care.

Table 5.3 Comparison of Outcomes Between Early and Late Biological Users

	Early vs. Late Biological Users	
Outcome Variables	Estimate (95% CI)	Model specifications
Net payment of all services, $	7.7% (3.0%,12.5%)*	GEE, gamma, log link
Net payment of inpatient services, $	-32.2% (-48.9%, -15.6%)§	GEE, gamma, log link
Net payment of outpatient services, $	-3.6% (-10.5%, 3.4%)	GEE, gamma, log link
Net payment of ER services, $	-15.9% (-32.3%, 0.5%)	GEE, gamma, log link
Net payment of prescription services, $	26.4% (22.1%, 30.7%)§	GEE, gamma, log link
Any use of inpatient services	0.57 (0.51, 0.64)§	Logistic regression
Any use of emergency room services	0.77 (0.69, 0.86)§	Logistic regression
Number of inpatient visits	-34% (-43%, -25%)§	GEE, Poisson, log link
Number of days of inpatient stay	-28% (-32%, -24%)§	GEE, Poisson, log link
Number of ER visits	-17% (-28%, -5%)†	GEE, gamma, log link
Number of outpatient visits	-0.3% (-4%, 3%)	GEE, gamma, log link
Number of prescriptions	-50% (-54%, -45%)§	GEE, gamma, log link

§: $p<0.001$, †: $p<0.01$, *: $p<0.05$

Figure 5.2 Proportion of Biological Users from 2005 to 2009

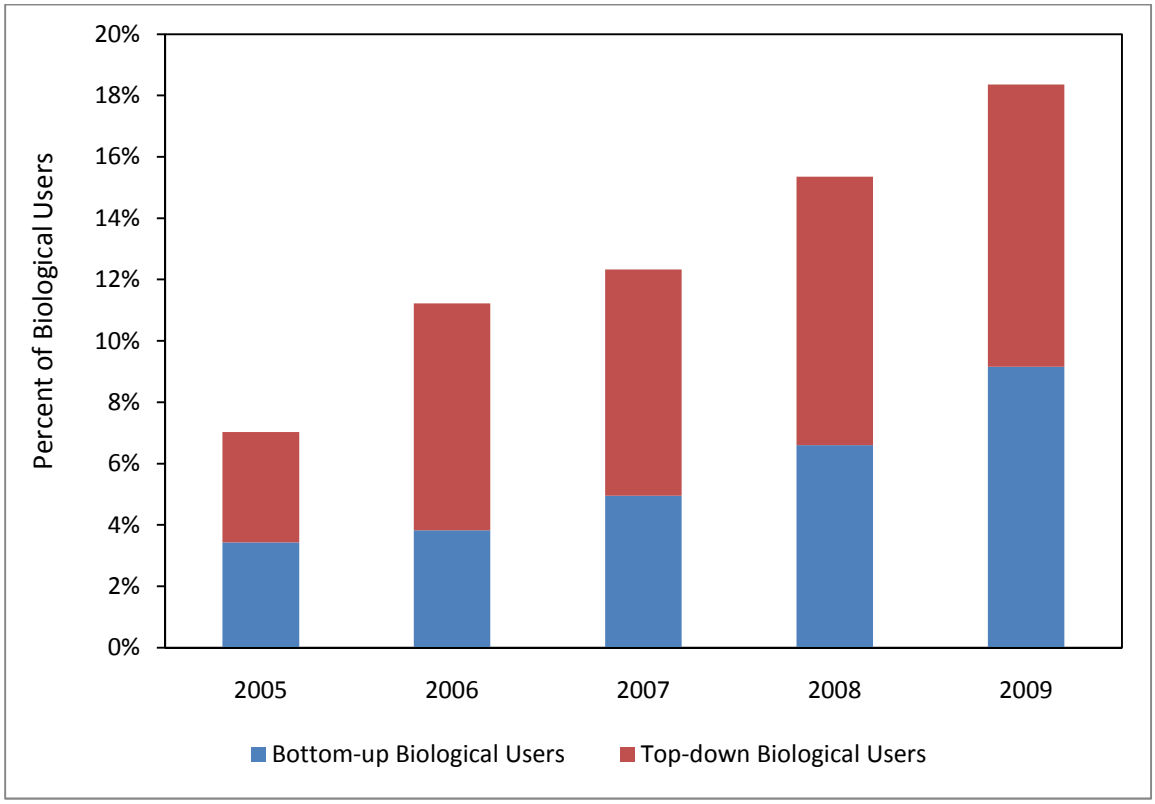
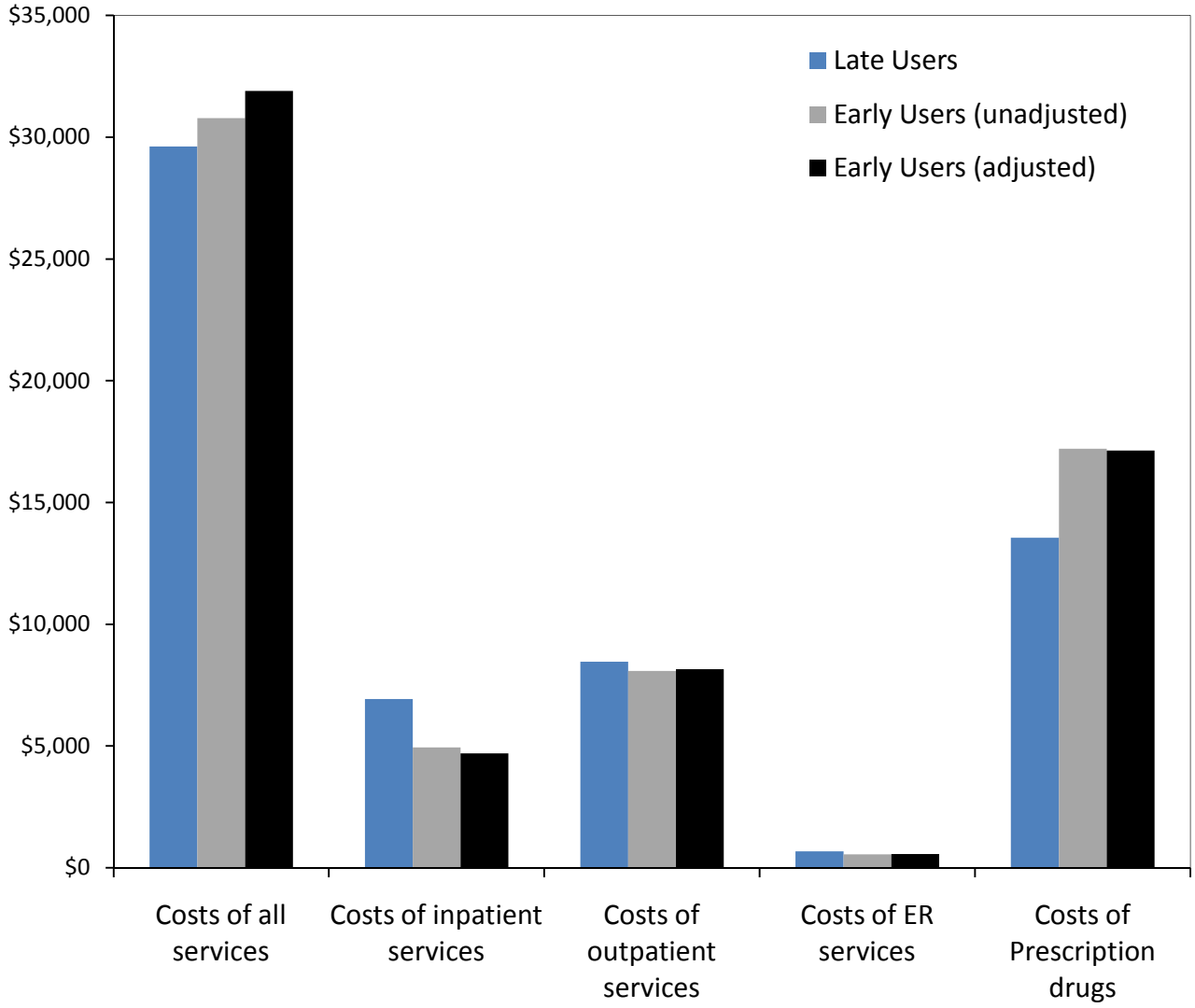


Figure 5.3 Comparison of Healthcare Costs for Early and Late Biological Users



APPDENDIX

Appendix Table 5.1 Prevalent Biological Users among Crohn's Disease Patients

Year	Eligible CD Patients	Biological Users	Percentage
2005	6,783	477	7.0%
2006	15,044	1,688	11.2%
2007	19,973	2,463	12.3%
2008	29,438	4,521	15.4%
2009	26,546	4,873	18.4%
Total	33,428	6,068	18.2%

Appendix Table 5.2 Use of Biological Agents from 2005 to 2009

	Number of infusions or injections				
Year	All biologics	Infliximab	Adalimumab	Natalizumab	Certolizumab pegol
2005	1,910	1,881 (98.5%)	29 (1.5%)	n/a	n/a
2006	7,206	7,033 (97.6%)	173 (2.4%)	n/a	n/a
2007	9,675	8,206 (84.8%)	1,469 (15.2%)	n/a	n/a
2008	20,946	13,329 (63.6%)	7,322 (35.0%)	120 (0.6%)	175 (0.8%)
2009	23,775	12,692 (53.4%)	9,804 (41.2%)	124 (0.5%)	1,155 (4.9%)
Total	63,512	43,141 (67.9%)	18,797 (29.6%)	244 (0.4%)	1,330 (2.1%)

n/a= not available. Both Natalizumab and Certolizumab pegol were approved by the FDA in 2008.

Appendix Table 5.3 Use of Biological Agents for Early and Late Biological Users

Biological Agent	Early Biological Users (N=3,082)	Late Biological Users (N=2,986)	Total (N=6,068)
Infliximab	2,669 (86.6%)	1,763 (59.0%)	4,432 (73.0%)
Adalimumab	638 (20.6%)	1,348 (45.1%)	1,982 (32.7%)
Natalizumab	15 (0.5%)	12 (0.4%)	27 (0.4%)
Certolizumab pegol	76 (2.5%)	210 (7.0%)	286 (4.7%)
Two biological agents	289 (9.4%)	311 (10.4%)	600 (9.9%)
Three biological agents	10 (0.3%)	18 (0.6%)	28 (0.5%)
Four biological agents	1 (<0.1%)	0 (0.0%)	1 (<0.1%)

Appendix Table 5.4 Odds Ratios Estimated by Logistic Regression Models

Independent Variables	Binary Variables	
	1= Biological Users 0=Non-biological Users	1=Early Biological Users 0=Late Biological Users
Age at diagnosis (numeric)	0.97 (0.97, 0.98)§	1.01 (1.00, 1.01)†
Female vs. male	0.94 (0.89, 1.00)*	1.00 (0.89, 1.11)
Diagnosis by GI specialist vs. non-specialist	1.13 (1.06, 1.21)§	0.97 (0.85, 1.09)
Geographic region		
Northeast vs. South	0.88 (0.80, 0.96)†	1.12 (0.94, 1.34)
North Central vs. South	0.90 (0.84, 0.97)†	1.03 (0.90, 1.17)
West or unknown vs. South	0.88 (0.80, 0.97)†	1.00 (0.83, 1.22)
MSA vs. non-MSA	1.10 (1.01, 1.20)*	1.24 (1.06, 1.46)†
Health plan vs. Large employers	1.33 (1.20, 1.47)§	2.10 (1.69, 2.60)§
PPO vs. other benefit plans	1.01 (0.94, 1.08)	1.21 (1.06, 1.38)†
Fulltime employee vs. others	0.86 (0.78, 0.96)†	0.73 (0.59, 0.91)†
Employee vs. spouse/dependent	0.96 (0.91, 1.03)	0.90 (0.80, 1.01)
CCI (numeric)	0.71 (0.64, 0.79)§	1.04 (0.84, 1.29)
Rx prior to diagnosis (numeric)	0.91 (0.90, 0.92)§	0.83 (0.80, 0.85)§
Year of diagnosis		
2006 vs 2005	1.34 (1.23, 1.47)§	2.05 (1.70, 2.47)§
2007 vs 2005	1.04 (0.93, 1.15)	1.31 (1.06, 1.61)*
2008 vs 2005	1.33 (1.21, 1.44)§	1.72 (1.45, 2.06)§
2009 vs 2005	0.78 (0.59, 1.03)	1.25 (0.70, 2.24)

MSA: metropolican statistical area, GI: gastroenterologist, PPO: preferred provider organization, CCI: Charlson comorbidity index

§: $p<0.001$, †: $p<0.01$, *: $p<0.05$

Appendix Table 5.5 Odds Ratios Estimated by Logistical Regression Models on Healthcare Utilization

Independent Variables	Binary Outcome Variables	
	Any use of inpatient services	Any use of emergency room services
Early vs. Late use	0.57 (0.51, 0.64)§	0.77 (0.69, 0.86)§
Age at diagnosis (numeric)	1.00 (1.00, 1.01)	1.00 (0.99, 1.00)
Female vs. male	1.28 (1.15, 1.43)§	1.26 (1.13, 1.40)§
Diagnosis by GI specialist vs. non-specialist	0.74 (0.66, 0.83) §	0.81 (0.72, 0.90)§
Geographic region		
Northeast vs. South	0.82 (0.69, 0.98) *	1.31 (1.10, 1.56)†
North Central vs. South	0.98 (0.86, 1.10)	0.97 (0.86, 1.10)
West or unknown vs. South	0.81 (0.67, 0.97)*	1.00 (0.83, 1.20)
MSA vs. non-MSA	1.01 (0.87, 1.18)	0.98 (0.84, 1.14)
Health plan vs. Large employers	1.05 (0.85, 1.29)	0.97 (0.79, 1.18)
PPO vs. other benefit plans	0.95 (0.83, 1.07)	1.00 (0.88, 1.13)
Fulltime employee vs. others	1.02 (0.83, 1.25)	0.92 (0.75, 1.11)
Employee vs. spouse/dependent	0.94 (0.84, 1.05)	0.97 (0.87, 1.09)
CCI (numeric)	1.49 (1.21, 1.83) §	1.46 (1.10, 1.94)†
Rx prior to diagnosis (numeric)	1.03 (0.02, 1.04) §	1.04 (1.02, 1.05)§
Year of diagnosis		
2006 vs 2005	0.93 (0.78, 1.11)	0.98 (0.82, 1.17)
2007 vs 2005	0.77 (0.63, 0.93)†	0.88 (0.73, 1.07)
2008 vs 2005	0.59 (0.50, 0.69)§	0.70 (0.59, 0.82)§
2009 vs 2005	0.46 (0.27, 0.81)†	0.64 (0.38, 1.08)

MSA: metropolican statistical area, GI: gastroenterologist, PPO: preferred provider organization, CCI: Charlson comorbidity index

§: $p<0.001$, †: $p<0.01$, *: $p<0.05$

Appendix Table 5.6 Effects Estimated by GEE Regression Models on Costs for Biological Users

Independent Variables	Outcome Variables				
	Net payment of all services, $	Net payment of inpatient services, $	Net payment of outpatient services, $	Net payment of ER services, $	Net payment of prescription services, $
Early vs. Late use	0.077 (0.030, 0.125)*	-0.322(-0.489,-0.156)§	-0.036(-0.105, 0.034)	-0.159(-0.323,0.005)	0.264(0.221, 0.307)§
Age at diagnosis (numeric)	0.005(0.003, 0.007)§	0.003(-0.003, 0.010)	0.01 (0.01, 0.01)§	-0.01 (-0.02, -0.00)§	0.004 (0.002, 0.006)§
Female vs. male	-0.04 (-0.09, 0.01)	0.01(-0.14, 0.17)	0.10 (0.03,0.16)†	0.20 (0.05, 0.35)*	-0.13 (-0.17, -0.09)§
Diagnosis by GI vs. non-specialist	-0.16 (-0.20, -0.11)§	-0.50 (-0.67, -0.33)§	-0.30 (-0.37, -0.22)§	-0.18 (-0.35, -0.02)*	0.02 (-0.01, 0.07)
Geographic region					
Northeast vs. South	0.07 (-0.0, 0.15)	-0.13 (-0.38, 0.12)	0.01 (-0.10, 0.12)	0.01 (-0.23, 0.25)	0.17 (0.10, 0.24)§
North Central vs. South	0.01 (-0.03, 0.07)	-0.12(-0.30, 0.06)	0.04 (-0.04, 0.11)	-0.14 (-0.31, 0.04)	0.04 (-0.01, 0.08)
West or unknown vs. South	0.08 (-0.0, 0.15)	0.04 (-0.23, 0.30)	0.05 (-0.06, 0.16)	0.31 (0.05, 0.56)*	0.10 (0.03, 0.17)†
MSA vs. non-MSA	-0.02(-0.08, 0.05)	-0.001(-0.22, 0.22)	-0.09 (-0.18, 0.00)	-0.001(-0.22, 0.22)	0.04 (-0.02, 0.10)
Health plan vs. Large employers	0.02(-0.07, 0.10)	0.26 (-0.02, 0.55)	-0.05 (-0.17, 0.08)	0.23 (-0.06, 0.50)	-0.02 (-0.09, 0.06)
PPO vs. other benefit plans	-0.03 (-0.08, 0.03)	-0.07(-0.25, 0.12)	-0.004 (-0.08, 0.07)	0.05 (-0.14, 0.23)	-0.03 (-0.07, 0.02)
Fulltime employee vs. others	0.09 (0.01, 0.17)*	0.19 (-0.08, 0.46)	-0.002 (-0.12, 0.12)	0.07 (-0.19, 0.34)	0.13 (0.05, 0.20)†
Employee vs. spouse/dependent	0.02(-0.03, 0.06)	0.01 (-0.15, 0.17)	-0.008 (-0.08, 0.06)	-0.09 (-0.25, 0.06)	0.04(-0.00, 0.08)
CCI (numeric)	0.14 (0.06, 0.22)*	0.40 (0.10, 0.71)*	0.18 (0.08, 0.29)†	0.27 (-0.02, 0.57)	0.003 (-0.07, 0.08)
Rx prior to diagnosis (numeric)	0.011(0.006, 0.016)§	0.02(0.00, 0.04)*	0.011(0.004, 0.019)†	0.037 (0.02, 0.06)§	0.002(-0.002, -0.007)
Year of diagnosis					
2006 vs 2005	0.01 (-0.06, 0.09)	-0.24 (-0.50, 0.01)	-0.04 (-0.14, 0.08)	0.01 (-0.23, 0.25)	0.15 (0.08, 0.21)§
2007 vs 2005	0.07 (-0.01, 0.15)	-0.07 (-0.35, 0.21)	-0.06 (-0.18, 0.06)	0.25 (-0.02, 0.53)	0.17 (0.10, 0.25)§
2008 vs 2005	0.21 (0.14, 0.28)§	0.04 (-0.20, 0.28)	0.14 (0.04, 0.24)†	0.35 (0.11, 0.58)†	0.30 (0.24, 0.37)§
2009 vs 2005	0.09 (-0.14, 0.31)	-0.25(-1.02, 0.53)	0.03 (-0.29, 0.36)	0.35 (-0.41, 1.10)	0.21 (0.01, 0.41)*
Intercept	9.97 (9.83, 10.12)§	8.68 (8.20, 9.16)§	8.74 (8.54, 8.94)§	6.52 (6.05, 6.99)§	9.07(8.93, 9.20)§
GEE model: variance function:	Gamma	Gamma	Gamma	Gamma	Gamma
link function:	log	log	log	log	log

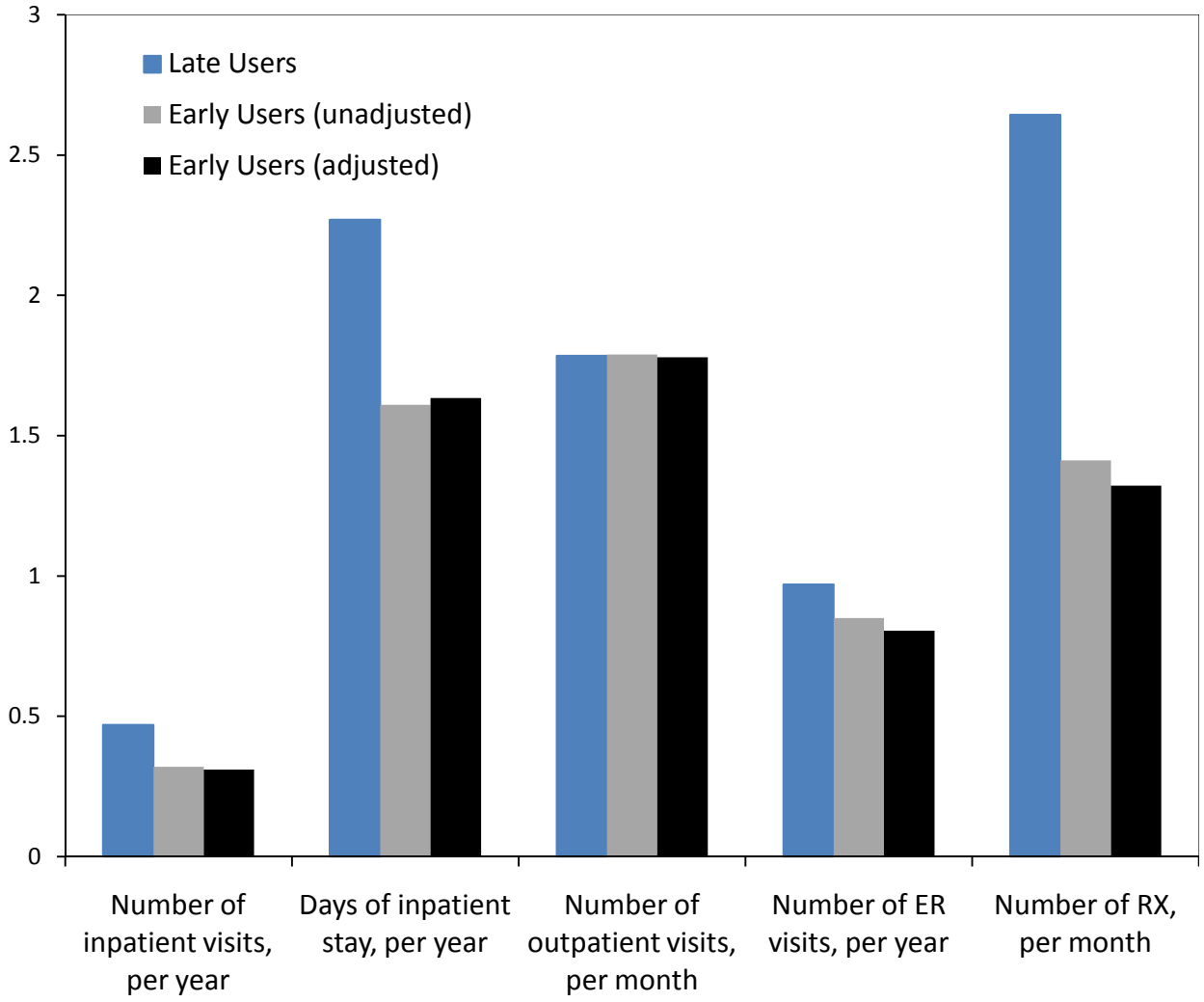
All costs are adjusted to 2010 US dollar ($) with annual CPI inflation rate of medical care.
MSA: metropolican statistical area, GI: gastroenterologist, PPO: preferred provider organization, CCI: Charlson comorbidity index
§: p<0.001, †: p<0.01, *: p<0.05

Appendix Table 5.7 Effects Estimated by GEE Regress Model on Healthcare Utilization of Biological Users

Independent Variables	Estimation (95% confidence interval) of Outcome Variables				
	# of inpatient visits	# of days of inpatient stay	# of ER visits	# of outpatient visits	# of prescriptions
Early vs. Late use	-0.34 (-0.43, -0.25)§	-0.28 (-0.32, -0.24)§	-0.17 (-0.28, -0.05)†	-0.003 (-0.04, 0.03)	-0.50(-0.54, -0.45)§
Age at diagnosis (numeric)	0.001 (-0.002, 0.004)	0.005 (0.003, 0.006)§	-0.008(-0.012, -0.003)†	0.01(0.01,0.01)§	0.014(0.012,0.016)§
Female vs. male	0.10 (0.02, 0.18)†	0.07 (0.04, 0.11)§	0.14 (0.03, 0.25)*	0.24 (0.20, 0.27)§	0.21(0.16, 0.25) §
Diagnosis by GI vs. non-specialist	-0.35 (-0.44, -0.25)§	-0.44 (-0.48, -0.39)§	-0.19 (-0.30, -0.07)†	-0.07(-0.11,-0.03)§	-0.003 (-0.05, 0.05)
Geographic region					
Northeast vs. South	-0.11 (-0.25, 0.03)	-0.21 (-0.27, -0.16)§	0.15(0.03, 0.32)	0.12 (0.06, 0.18)§	-0.15 (-0.21, -0.08)§
North Central vs. South	-0.06(-0.15, 0.03)	-0.18 (-0.22, -0.13)§	-0.22 (-0.34,-0.10)§	0.04(0.001, 0.8)*	-0.06(-0.11, -0.01)*
West or unknown vs. South	-0.22 (-0.37, -0.08)†	-0.35 (-0.41, -0.28)§	-0.04 (-0.22, 0.14)	0.05 (-0.01, 0.11)	-0.04 (-0.12, 0.03)
MSA vs. non-MSA	-0.11 (-0.22, 0.01)	-0.05(-0.10, 0.003)	-0.08 (-0.24, 0.07)	0.04 (-0.01, 0.09)	-0.01(-0.08, 0.05)
Health plan vs. Large employers	0.09 (-0.07, 0.25)	0.06 (-0.01, 0.13)	0.17 (-0.04, 0.37)	0.08(0.01, 0.14)*	-0.23 (-0.31, -0.15)§
PPO vs. other benefit plans	-0.003 (-0.10, 0.09)	0.0003(-0.04, 0.04)	0.07 (-0.06, 0.20)	0.03(-0.01, 0.07)	-0.06(-0.11,-0.004)*
Fulltime employee vs. others	0.08 (-0.07, 0.24)	0.02 (-0.05, 0.09)	-0.06 (-0.26, 0.13)	0.02 (-0.05, 0.08)	0.07 (-0.01, 0.14)
Employee vs. spouse/dependent	-0.09 (-0.17, 0.001)	-0.05 (-0.08,-0.01)*	-0.11 (-0.22,-0.01)*	-0.02 (-0.06, 0.01)	-0.03 (-0.07, 0.02)
CCI (numeric)	0.25 (0.17, 0.33)§	0.24 (0.20, 0.28)§	0.24 (0.04, 0.44)*	0.19 (0.12, 0.25)§	0.07 (-0.005, 0.14)
Rx prior to diagnosis (numeric)	0.02 (0.02, 0.03)§	0.02 (0.02, 0.03)§	0.03 (0.02, 0.04)§	0.02 (0.01, 0.02)§	0.04 (0.03, 0.04)§
Year of diagnosis					
2006 vs 2005	0.02 (-0.11, 0.16)	-0.12 (-0.19,-0.06)§	0.10 (-0.07, 0.28)	0.14 (0.08, 0.20)§	-0.05 (-0.12, 0.03)
2007 vs 2005	0.14 (-0.005, 0.29)	0.05 (-0.02, 0.12)	0.22(0.03, 0.42)*	0.12 (0.06, 0.19)§	0.23 (0.15, 0.31)§
2008 vs 2005	0.19 (0.06, 0.31)†	0.15 (0.10, 0.21)§	0.36 (0.20, 0.53)§	0.17 (0.11, 0.22)§	0.21 (0.15, 0.28)§
2009 vs 2005	0.25 (-0.12, 0.63)	-0.07 (-0.26, 0.12)	0.30 (-0.33, 0.35)	0.15(-0.03,0.33)	0.17 (-0.05, 0.39)
Intercept	-0.83 (-1.10, -0.56)§	0.73 (0.61, 0.85)§	0.01 (-0.33, -0.35)	2.19 (2.08, 2.31)§	2.72 (2.58, 2.86)§
GEE model: variance function:	Poisson	Poisson	Gamma	Gamma	Gamma
link function:	log	log	log	log	Log

MSA: metropolican statistical area, GI: gastroenterologist, PPO: preferred provider organization, CCI: Charlson comorbidity index
§: p<0.001, †: p<0.01, *: p<0.05

Appendix Figure 5.1 Comparison of Healthcare Utilization between Early and Late Biological Users



CHAPTER VI:

BUDGET IMPACT OF TREATMENT STRATEGY CHANGE ON PATIENTS WITH CROHN'S DISEASE FROM PAYERS' PERSPECTIVE

Background: The treatment strategy for Crohn's Disease (CD) has recently undergone a significant shift toward a 'top-down' strategy by adopting biological therapies early to aggressively manage this disease. This shift in treatment strategy may challenge pharmacy benefits management organizations (PBMOs) managing prescription drug costs for these expensive treatments.

Objectives: This study seeks to predict the budgetary impact of the change in prescription drug costs resulting from the top-down treatment approach to PBMOs.

Methods: A decision tree model was constructed to compare prescription drug costs of top-down versus bottom-up strategy for biological therapies in the first, second, and third year following CD diagnosis. Top-down therapy was defined as a treatment approach where biological therapy was included in the first-line treatment for CD patients. Bottom-up therapy referred to use of novel biological therapies after conventional non-biological drugs were attempted. Transition probabilities and prescription drug costs were modeled by disease severity using claims data of biological users in the MarketScan Commercial Claims and Encounter database from 2005 to 2009.

Results: In the first year of CD diagnosis, top-down therapy resulted in an increase of $9,235 in prescription drug costs, compared with the bottom-up approach. The difference in

prescription drug costs was reduced to $2,064 in the second year and $1,576 in the third year. Meanwhile, in the second and third years, a higher percentage of patients following the bottom-up approach experienced more severe disease.

Conclusion: The top-down treatment strategy for CD management resulted in a higher prescription drug costs during the first year of treatment. These results diminished over the second and third years as bottom-up users began using biological therapies. Further study is needed to demonstrate whether or not the top-down treatment approach is cost-saving when total healthcare costs are accounted for.

6.1 Introduction

The treatment strategy for Crohn's disease (CD) is currently changing in clinical practice.[83] A new treatment approach that promotes early use of biological therapies in the CD treatment algorithm has been suggested to have greater therapeutic benefits than conventional treatments for CD management.[12, 13] Previously, CD patients were treated with aminosalicylates, antibiotics, corticosteroids, and immunomodulators before being initiated on biological therapies.[11] However, response rates from these conventional drugs were low, and most CD patients underwent surgeries or became steroid dependent.[29] Biological drugs have many therapeutic benefits when compared to conventional medications in the treatment of CD, including a higher response rate, more rapid onset of clinical response, greater effectiveness in maintaining long-term remission, and significant improvement in health related quality of life.[7, 8, 29, 84, 85] Due to their high costs, biological therapies are typically reserved as the last medical resort for patients who are

refractory or intolerant to conventional drugs. This treatment strategy, referred to as 'bottom-up' approach, advocates that patients start with less expensive drugs, and gradually move to more advanced therapies. Recently, clinical studies have shown that biological therapies have a more rapid remission and higher remission rate if they are introduced into the treatment algorithm early in the disease course. Thus, a new treatment strategy, referred to as 'top-down' approach, suggests that patients start with biological therapy as first-line treatment, either in combination with immunomodulators or as mono-therapy. The top-down approach has become the preferred treatment approach for CD disease management and, as a result, the use of biological therapies is expected to increase. This raises concerns about a surge in drug expenditures for both patients and payers in treating CD.

One group that is particularly interested in the changing treatment strategy for CD is pharmacy benefit management organizations (PBMOs). In the U.S. healthcare system, PBMOs play a pivotal role in negotiating price with manufacturers, purchasing discounted drugs, and distributing and administering drugs to patients. Today more than 95% of consumers receive pharmaceutical drug benefits though a PBMO.[86] PBMOs can be separate organizations, or affiliated with managed care organizations (MCOs), which are major payers in the private insurance sector. As healthcare becomes more complex and costly, PBMOs have expanded their functions from drug vendors to collaborative partners with MCOs in the effort to improve quality of care and safety and to control expenses for prescription drugs.[87] In the past decade, the rapid expansion of biological drugs in the pharmaceutical market poses extraordinary challenges for PBMOs mainly because of high costs associated with biological drugs. Additionally, biological drug therapies raise complex issues in drug distribution, administration and access, so that specialty pharmacy programs

are developed within PBMOs to provide extended services for payers, who are mostly MCOs in the private insurance sector. More importantly, MCOs are facing challenges to manage rising drug costs as biological drugs cost anywhere from $10,000 to $200,000 per member per year.[67]

CD is a chronic disease that incurs substantial medical costs to patients. In our previous study, we found that the annual costs for prescription drugs averaged $16,848 for each patient who used any biological therapies (see Chapter 5). The treatment strategy change for CD patients is anticipated to escalate the costs for PBMOs because biological therapies are introduced earlier in the course of the disease.[88] The budgetary impact of the change in prescription drug costs resulting from aggressive top-down therapy in CD treatment strategy to PBMOs is unknown.

In this study, a decision tree was modeled to compare prescription drug costs between patients who use top-down and bottom-up approaches. The budget impact was represented by the difference in drug costs for CD patients who initiated biological therapy following either the top-down or bottom-up approach three years after their initial diagnosis of Crohn's disease. Predictions from the decision model were based on empirical, real-world data estimates from a prior cohort study using MarketScan Commercial Claims and Encounter database from 2005 to 2009. Finally, sensitivity analysis was conducted to test the robustness of the predicted budget impact on pharmacy benefit programs. Results from this study provide important information for pharmacy benefit managers to consider when making formulary decisions.

6.2 Methods

Decision Modeling

A decision tree was developed to compare prescription drug costs for CD patients who used biological therapies following the top-down and bottom-up treatment approaches (see Figure 6.1). The perspective of this analysis was a broader view of PBMOs, so prescription drug costs included both: a) drug payments that were made by PBMOs, on behalf of payers, to pharmacies; and b) drug payments that were directly paid by payers under medical benefit because biological therapies can be administered other places (e.g. infusion center). Given our perspective on payers, out-of-pocket (OOP) costs to patients and coordination of benefit (COB) payments from other payers were excluded.

Disease severity is a key factor that prompts medical and surgical treatment decisions in CD management, and further determines the amount of healthcare services for CD patients. Changes in disease severity also reflect the outcomes of the medical treatments that patients received previously. A time frame of three years following CD diagnosis was included in the model. Disease severity was evaluated on an annual basis. In each year, disease severity was assessed according to patients' healthcare utilization records, and classified into one of four categories: a) remission; b) mild to moderate; c) moderate to severe; or d) severe or fulminant. Initial pathways depicted on the decision tree for each treatment strategy show disease severity in the first year following CD diagnosis. Disease severity for CD patients was either changed from the first year to the second year, or remained the same. A transition in disease severity from the first year to the second year is demonstrated by the pathways in the second layer of the decision tree. To populate the decision model, cohort analyses were conducted to estimate prescription drug costs (payoff value) and the transition probabilities

for all pathways. Under top-down scenario, the probability of severity allocation and cost assignment of each classification of severity were based on the estimation from patients who adopted biological therapies in their initial CD treatment in a large claims database from 2005 to 2009. For patients under bottom-up scenario, their model parameters were estimated from patients who used biological therapies later than conventional drugs in the same database. Probabilistic sensitivity analysis (PSA) using Monte Carlo simulation was performed to quantify the impact of uncertainties in input parameters on the uncertainty in model output. Both base-case and sensitivity analyses were conducted in TreeAge Pro 2011 (TreeAge Software Inc., Williamstown, MA). The study was approved by the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill.

Data Source and Patient Cohorts

The MarketScan Commercial Claims and Encounter (CCAE) database (Thomson Reuters, Ann Arbor, Michigan) served as the primary data source for this study. CCAE data are comprised of pharmacy and medical claims from January 1, 2005 to December 31, 2009. The CCAE database captured person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services from approximately 100 payers, including large employers and health plans.

In the CCAE database, a total of 33,428 CD patients met the following inclusion criteria: age between 18 and 64; a minimum of one year enrollment after CD diagnosis; a six-month washout period prior to diagnosis; managed care organization enrollee; and at least one CD-related prescription fill. Among these eligible CD patients, 18.2% (n=6,068) received at least one infusion or injection of an FDA-approved biological agent, including

infliximab, adalimumab, natalizumab, or certolizumab pegol. There were 3,082 patients who included biological therapy early as first-line treatment in their disease course, and 2,986 patients who used biological agents later after attempting other non-biological therapies. These early and late biological therapy users were considered using top-down and bottom-up treatment strategy, respectively. All cost parameters and probabilities in the decision analyses were estimated based on the utilization and cost information for CD patients in these two study cohorts: early and late biological users.

Disease Severity Classification

Disease severity in the first year of diagnosis and the following two years was imputed indirectly according to each patient's healthcare utilization. Disease severity was approximated given a lack of relevant clinical information in the claims database. In clinical practice, CD is often classified according to the Crohn's Disease Activity Index (CDAI), an instrument used to quantify disease symptoms (e.g., the number of liquid or soft stools each day for seven days) through weighted numeric scores. This classification algorithm is commonly referred to in disease management guidelines, but not readily available in claims databases. The MarketScan CCAE database contains a broad spectrum of person-specific clinical utilization and financial information, but includes limited medical information, such as diagnosis. In pursuit of a practical approach, Malone et al. developed an algorithm that used pharmaceutical and medical claims to classify CD patients into four severity categories. The pharmacy and medical information that was used to classify disease severity were based on the American College of Gastroenterology (ACG) criteria (See Appendix Table 6.1).

In this study, disease severity was evaluated annually according to Malone et al.'s algorithm by reviewing all pharmacy and medical claims incurred in a given year (see Appendix Table 6.1). Claims were examined for criteria in each severity category from the highest (severe/fulminant) to lowest (remission) severity. For patients with multiple claims, disease severity was determined by those ones in the definition of the highest severity. When no claims matched the criteria for a higher severity category, the next lower category was considered. Patients who had no claims filed in a given year were assumed to have achieved disease remission.

Probabilities

Probabilities for disease severity in the first year of CD were based on proportions of biological users in different severity categories classified according to their claims data in the first year following diagnosis. From 2005 to 2009, 23.7% of biological users (N=6,068), including both early (N=3,082) and late biological users (N=2,986), had severe/fulminant disease in the first year following diagnosis, 41.0% were classified with moderate-severe disease, 11.7% had mild-moderate disease, and 23.6% were in disease remission (see Table 6.1).

Transition probabilities for disease severity from the first year of CD to the second year were estimated by transition patterns of biological users who had at least two years of follow-up data. For example, among late biological users, 1,961 CD patients had two or more years of claims data, including 497 patients with severe/fulminant disease in the first year of CD diagnosis. Of these patients, 64 (12.9%) achieved disease remission, 61 (12.3%) patients had mild-moderate disease, 182 (36.6%) had moderate-severe disease, and 190 (38.2%)

continued to experience severe/fulminant disease in the second year. Therefore, under bottom-up scenario, the transition probabilities of disease severity from the first year to the second year are 0.129 for patients changing from severe/fulminant to remission, 0.123 from severe/fulminant to mild-moderate, 0.366 from severe/fulminant to moderate-severe and 0.382 for patients remaining to have severe/fulminant disease (see Table 6.1). Similarly, transition probabilities for disease severity from the second year of CD to the third year were estimated by transition patterns of biological users with complete data in the second and third year. In the calculation of transition probabilities, patients were required to have valid enrollment in both start and end years.

Prescription Drug Costs

Prescription drug costs for patients in each year following their diagnosis of CD were calculated by accumulating all payments made by payers directly through medical benefit reimbursement, or indirectly via PBMOs under pharmacy benefit. For conventional non-biological drugs, payers usually use a 'carve-out' model and contract with one or more PBMOs to manage their prescription benefit. Under the carve-out model, PBMOs make payments to pharmacies on behalf of payers. Pharmacy claims are adjudicated with NDC numbers, which are unique identifiers for each drug. Therefore, payments of all claims in the CCAE database with valid NDC numbers of all drugs, including CD- and non-CD-related drugs, represent the overall costs of pharmacy benefits for conventional drugs. Biological therapies, however, can be reimbursed under either the pharmacy benefit or medical benefit depending on the site and method of administration. All biological therapies for CD are office-administered injectables used intravenously (infliximab and natalizumab), or

subcutaneously (adalimumab and certolizumab pegol). If a biological therapy was administered at outpatient or inpatient visits, the claim is usually submitted with a healthcare common procedure coding system (HCPCS) 'J' code and reimbursed under medical benefits. Some specialty pharmacy management companies may be contracted to reimburse those claims through pharmacy benefits. But they were more often charged directly by providers using the 'buy and bill' model.[67].

The annual prescription cost is the average amount that payers reimbursed patients for prescription drugs used in each 12-month period after the CD diagnosis. For patients who were partially enrolled in MCOs during the second and third years of CD, their annual drug costs were annualized according to the length of enrollment. The annualized rate was calculated according to the proportion of prescription drug costs in each month over a one-year period for patients with a full-year of claims data. The annualized rate was not a fixed rate at 1/12, but instead, varied from month to month according to the incremental pattern of prescription drug costs for patients with complete one-year data. For example, if a patient only had 3 months of data available in the second year of disease, prescription drug cost of the second year for this patient was extrapolated by dividing the rate of drug cost in the first three months out of the entire second year for patients with two years of continuous enrollment. Prescription drug costs occurring in each calendar year were adjusted to the value of the U.S. dollar in 2010, and then calculated annually according to patients' treatment strategy and disease severity classification (see Table 6.2).

Base Case Analysis

The base case in the decision model refers to a new Crohn's disease patient who uses biological therapies following conventional 'bottom-up' strategy. The alternative case is the patient who instead uses biological therapies following new 'top-down' approach. Regardless of case scenario, the patient was assumed to have the same severity of disease as an average biological user during the first year of disease from 2005 to 2009. The prescription drug cost was estimated accordingly by disease severity and treatment strategy adapted during the disease course. In the second and third year of disease, patients were allocated transition probabilities for different disease severities. Base case analysis compared the prescription drug costs of the base case patient with the alternative case patient in the first three years of disease. The difference in costs of prescription drugs demonstrates the economic effect of new top-down treatment strategy.

Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) using Monte Carlo simulation was performed to estimate the impact from uncertainty regarding input parameters in the decision model. The input parameters, both transition probabilities and prescription drug costs, were each specified with different distributions. Given the complexity of multiple categories for disease severity, the Dirichlet distribution was used to represent the pattern of multinomial parameter probabilities. Although a series of conditional beta distributions could describe multinomial data, the Dirichlet distribution has been successfully implemented to ease in fitting multinomial probabilities in decision modeling. [71] For prescription drug costs, a gamma

distribution was used to describe its distribution given that costs are constrained on the interval 0 to positive infinity (see Appendix Table 6.2).

The probabilities for all classifications of disease severity are quite different between early and late biological users in their first year of disease. Compared to early biological adopters, late biological users are more likely to have moderate and severe disease. In the base case analysis, the probabilities for disease severity were based on the classification of all biological users pooled together. Considering both early and late biological users in the previous year as two extreme cases, scenario analyses were conducted to test whether or not study results are heavily determined by disease severity of the initial cohort. In Case Scenario 1, the probabilities for disease severity categories in the first year were based on the proportion of patients with different severities among late biological users in previous years. Probabilities for patients to have disease remission, mild-moderate disease, moderate-severe disease, and severe/fulminant disease in the first year after CD diagnosis were 0.046, 0.163, 0.516, and 0.275 respectively. In Case Scenario 2, the probabilities in the first year were based on patient distribution by severity among early biological users. Those probabilities for different disease severity categories, i.e., remission, mild, moderate-severe, and severe/fulminant, were 0.421, 0.072, 0.307 and 0.200, respectively.

6.3 Results

Base Case Analysis

In the first year following CD diagnosis, prescription drug costs were estimated at $18,166 if patients used the top-down treatment approach, and $8,945 if they used the

bottom-up approach. The new top-down treatment approach is associated with higher prescription drug costs, and was 103.8% higher than the costs for bottom-up patients with CD in the first year.

Prescription drug costs for CD patients in the second and third years are predicted at $17,109 and $15,752, respectively, if a patient used the top-down treatment strategy. These predicted values are 13.8% and 10.4% higher in the second and third year, respectively, than the costs for patients using the bottom-up treatment approach. The difference in prescription drug costs between the two treatment approaches is projected to lessen significantly in the second year of disease (see Table 6.3).

Sensitivity Analysis

Results of the probabilistic sensitivity analysis confirmed the findings that inform the base case analysis. The prescription drug costs for patients following top-down treatment approach were $9,235 higher than the costs for bottom-up therapy users in their first year of disease. The difference in prescription drug costs between the top-down and bottom-up biological users rapidly reduced to $2,064 and $1,476 in the second and third years, respectively (see Table 6.3).

Scenario analyses compared the results from two extreme cases, where disease severity in the first year was based on the data of either late biological users (Case Scenario 1) or early biological users (Case Scenario 2) in previous years. The difference in prescription drug costs between two treatment strategies was $7,720 in the first year of CD for Case Scenario 1, and $10,768 for Case Scenario 2. In the second and third year of CD, the differences in prescription drug costs decreased to $2,197 and $1,606 respectively for Case

Scenario 1, which were comparable to the results of Case Scenario 2 ($1,974 in the second year and $1,470 in the third year) and the results of base case ($2,064 and $1,476) (see Appendix Table 6.4).

6.4 Discussion

Our results suggest that new top-down treatment strategy with biological therapy is associated with substantially higher prescription drug costs than the conservative bottom-up treatment approach in the first year of CD. The dramatic difference in prescription drug costs can be attributed to the time preference for initiating biological therapies between the two treatment approaches. Patients that adopted biologics early by following top-down approach initiated biological therapy on average 89 days after CD diagnosis. However, patients following the bottom-up approach initiated their first biological therapy 365 days after CD diagnosis on average (data not shown).

The perspective of this analysis is PBMOs, who manage the pharmacy benefits for health plans, and reimburse drug costs to pharmacies on behalf of payers. Traditionally, PBMOs are only responsible for costs of the prescriptions that are delivered at the pharmacy. The rapid increase in the use of specialty drugs, (e.g., biological therapies), has changed the practice of PBMOs because specialty drugs are administered differently (e.g., intravenous infusion and subcutaneous injection) and at different sites (e.g., physician's office, infusion center, outpatient hospital department, and home). PBMOs have developed or acquired specialty pharmacy programs to cope with this change in the market place. Most payers include self-administered injectables (e.g., adalimumab and certolizumab pegol) in the

pharmacy benefit, and office-administered injectables (e.g., infliximab and natalizumab) in the medical benefit.[89] However, a small portion of biological drugs for CD did not follow the convention above due to a lack of a uniform coding system for drugs across pharmacy and medical benefits (see Appendix Table 6.3). Therefore, this study took a broader view of PBMOs, and included drug costs that were covered under both the pharmacy and medical benefit.

Our results showed that the difference in prescription drug costs between the two treatment approaches significantly reduced from $9,235 in the first year to $2,064 in the second year, and further fell to $1,476 in the third year of disease. This change was primarily caused by the rapid increase in prescription drug costs incurred by the bottom-up biological users, who began using biological therapies in the second and third years. It is worth noting that the prescription drug costs of top-down biological users decreased each year. Additional analyses were conducted to determine how much biological and non-biological therapies have contributed to the reduction in overall prescription drug costs. As shown in the summary of prescription drug costs for non-biological therapies in Appendix Table 6.4, it was found that top-down biological users incurred lower costs for non-biological drugs than bottom-up biological users in each of three years of CD. This could be explained by the cohort difference that late biological users had more comorbid conditions than early adopters. While conventional drug costs for top-down biological users remained unchanged in the first three years of disease, the conventional drug costs increased steadily for bottom-up biological users. The increased use of conventional drugs among bottom-up biological users may prevent prescription costs from decreasing as rapidly as top-down biological users. This could result in a reduction in the drug cost difference between these two treatment strategies

from the first year to third year and could result in the top-down treatment approach being cost saving to prescription drug budgets in the long term.

In this study, disease severity was used as an instrument to assess the outcome of medical treatments for CD, including biological therapies. Comparing allocation of CD patients by disease severity, we found that patients were more likely to have disease remission and less likely to have moderate to severe disease after the first year of CD if they followed the top-down treatment approach. From the transition probability matrix, the probability of having moderate-severe disease at the end of the first year was 0.41 for all biological users. At the end of the second and third years, the probability of moderate or severe disease decreased to 0.34 and 0.37 respectively for patients using top-down treatment approach. On the contrary, this probability increased to 0.49 and 0.50 for bottom-up users (see Figure 6.2). At the mean time, the probabilities of disease remission changed in a reversed pattern, while the probabilities of mild and severe/fulminant disease remained nearly unchanged between patients who used top-down and bottom-up treatment strategy. Subsequently, the current study demonstrates that patients who followed the top-down treatment approach had higher prescription drug costs in the first year than those using the bottom-up approach. These results suggest that, for patients using top-down approach, higher prescription drug costs were exchanged for positive clinical outcomes. In theory, positive clinical outcomes can improve patients' quality of life, and reduce health care utilization and overall healthcare costs in the long term. Further study is needed to demonstrate whether or not cost savings can be achieved with lower total healthcare costs for the top-down treatment approach.

While constructing the budget impact model, we made several assumptions:

First, we assumed that patients' characteristics, including age, gender, region, employment status, and insurance type, had no effect on patients' preference for treatment strategy. In a previous study conducted on this same population (see Chapter 5), we found that there was considerable difference in some patient characteristics, such as employment status, between the early and late biological users, but none of these variables were consistent predictors for healthcare utilization. These factors were not accounted for in our modeling because there was no adequate information in the claims database regarding detailed employment status (e.g., salary, and benefit plan).

Second, we assumed that health status and comorbid conditions had no effect on patients' choice of treatment strategy. According to CD management guidelines, biological therapies are recommended for patients with severe or refractory disease. However, we found more than half of biological therapy users included a biological therapy in their first-line treatment. This suggests that factors other than disease status and overall health condition may be responsible for treatment decisions. We noticed that disease severity was quite different between early and late biological users in the first year. For example, the probability of moderate-severe disease for late biological users is higher than early biological users (0.516 vs. 0.307). This difference may be caused by more prevalent use of immuno-modulators (e.g., azathioprine) among late users because the use of those drugs is an indicator of moderate-severe disease in the disease severity definition by Malone et al. To test the robustness of results in disease severity at baseline, we conducted case scenario analyses, and found that baseline disease severity has little effect on the difference in prescription drug costs in the second and third years between the early and late adoption treatment approaches (see Appendix Table 6.5).

Third, we assumed that disease severity does not frequently change for CD patients, and can be approximated by their healthcare utilization records. We used an empirical method developed by Malone et al. to classify patients into four different severity categories by using patients' medical and pharmacy claims. This method has not been verified in an actual patient population. It is unknown how accurate the definition of disease severity is when compared with standard way in clinical practice. There is likely a potential misclassification, particularly for patients with milder disease symptom. [68] However, the criteria used in the Malone algorithm for disease severity classification reflect current treatment practice in the US. Therefore, it is more relevant to actual CD management than previously published models, which were often based on patients in other healthcare systems.[52, 54] Our results showing patient allocation in each disease severity category is consistent Malone et al.'s results. Due to the lack of direct medical information to more precisely evaluate patients' disease progression, the algorithm proposed by Malone et al. was used as a reasonable proxy for severity classification in this study.

6.5 Summary

For newly diagnosed CD patients, top-down treatment approach resulted in an increase of $9,235 in prescription drug costs during patients' first year of CD, potentially having a substantial impact on pharmacy budgets to PBMOs. The incremental costs of prescription drugs was reduced to $2,064 in the second year and $1,476 in the third year. It is believed that higher prescription drug costs for patients who use the top-down treatment strategy could result in better clinical outcomes in the long term. Further study is needed to demonstrate whether or not the top-down biological strategy is cost-saving when total healthcare costs are accounted for.

Figure 6.1 Decision Tree (2-year model)

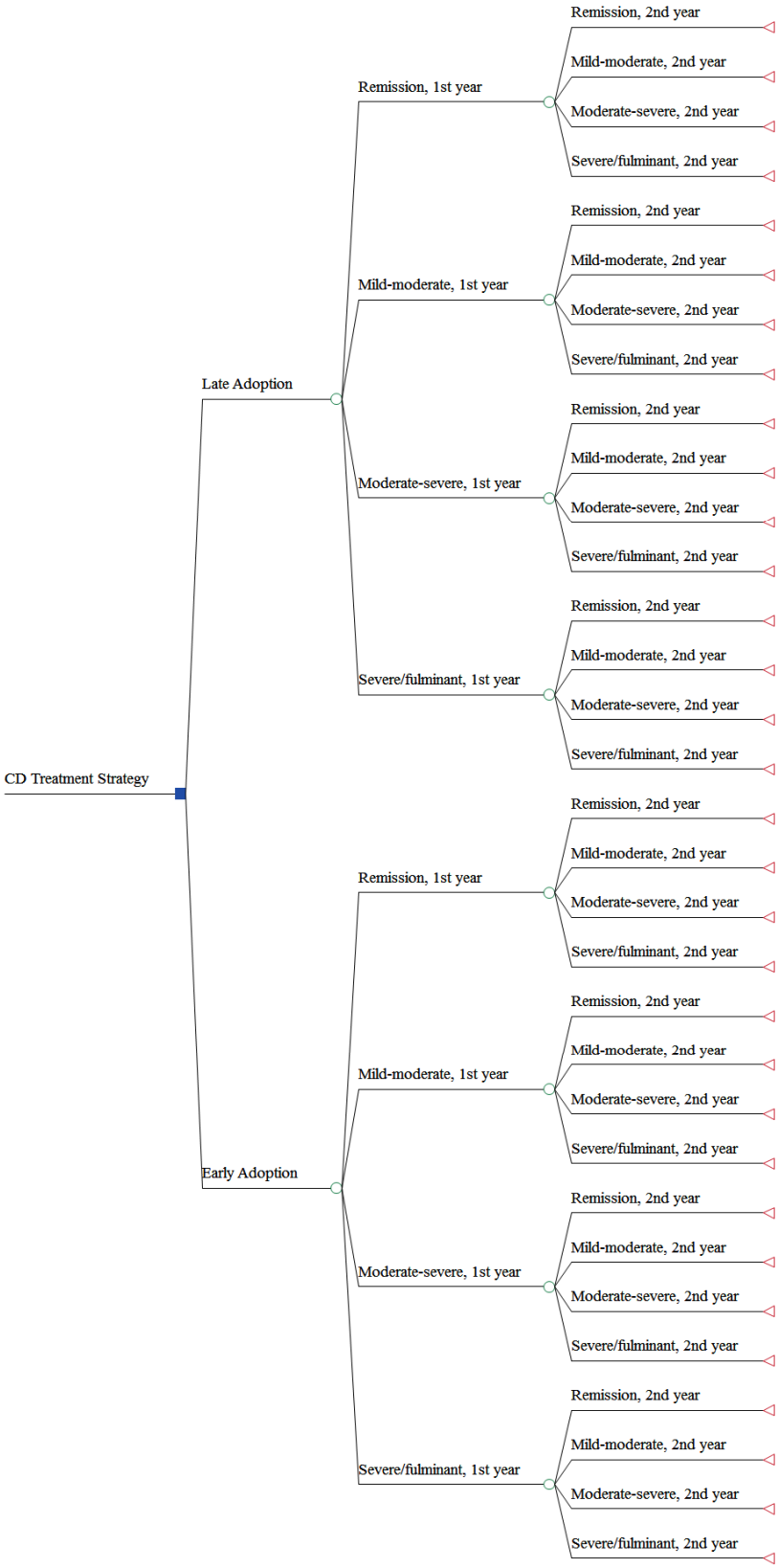


Figure 6.2 Comparison of Probabilities of Disease Severity in Three Years

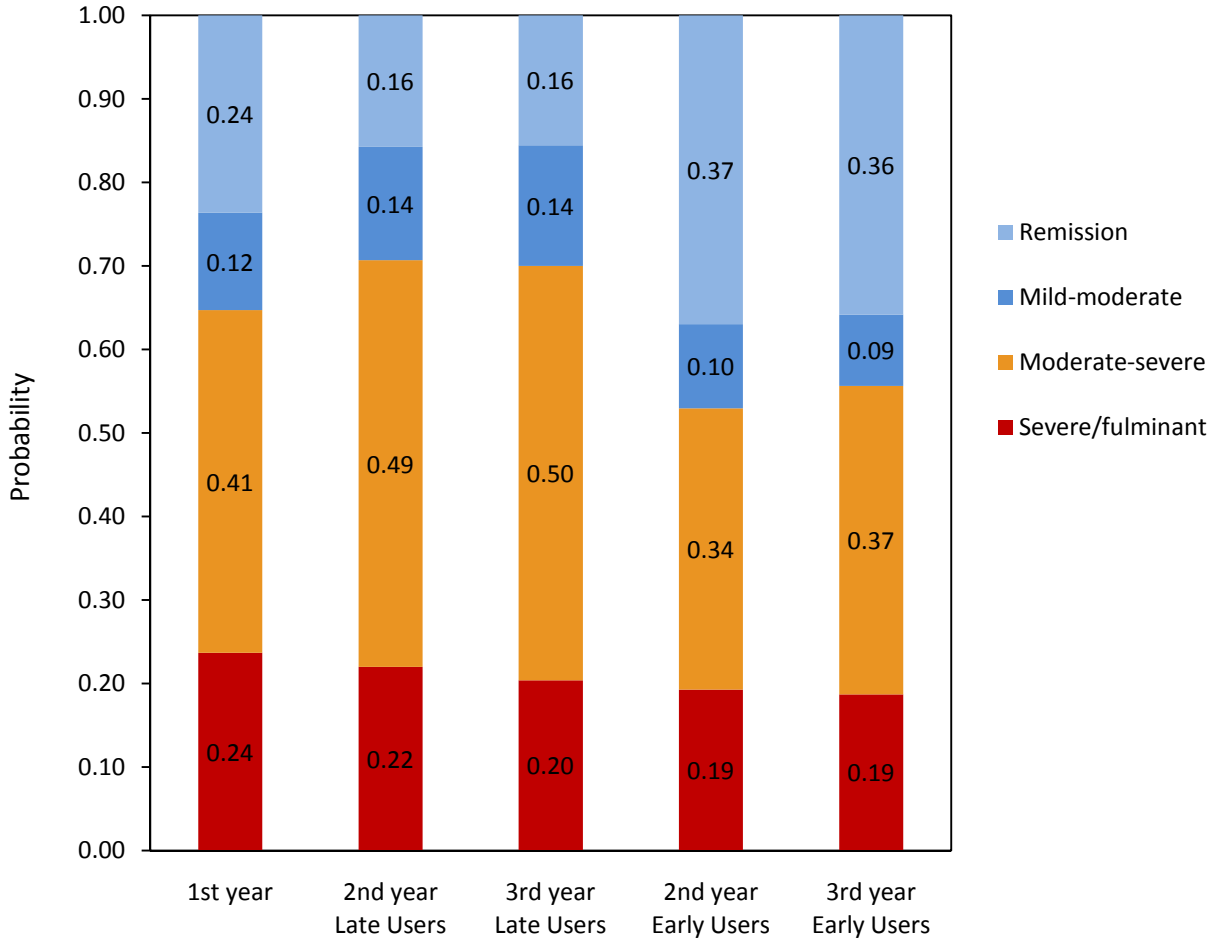


Table 6.1 Transition Probabilities

Year/Severity	Remission	Mild-moderate	Moderate-severe	Severe/Fulminant
Biological users:				
1st year after diagnosis	0.236	0.117	0.410	0.237
Late biological users:				
1st year			2nd year	
Remission	0.260	0.135	0.442	0.163
Mild-moderate	0.171	0.370	0.288	0.171
Moderate-severe	0.112	0.077	0.639	0.172
Severe/Fulminant	0.129	0.123	0.366	0.382
2nd year			3rd year	
Remission	0.436	0.188	0.265	0.111
Mild-moderate	0.147	0.410	0.282	0.161
Moderate-severe	0.090	0.081	0.691	0.138
Severe/Fulminant	0.105	0.089	0.363	0.443
Early biological users:				
1st year			2nd year	
Remission	0.690	0.054	0.151	0.105
Mild-moderate	0.289	0.386	0.228	0.097
Moderate-severe	0.250	0.074	0.549	0.127
Severe/Fulminant	0.297	0.054	0.210	0.439
2nd year			3rd year	
Remission	0.621	0.073	0.225	0.081
Mild-moderate	0.204	0.296	0.315	0.185
Moderate-severe	0.167	0.062	0.612	0.159
Severe/Fulminant	0.270	0.039	0.250	0.441

Table 6.2 Prescription Drug Costs by Disease Severity and Time after Diagnosis

Year/Severity	Remission	Mild-moderate	Moderate-severe	Severe/Fulminant
Late biological users (bottom-up strategy):				
1st year	$579($3,438)	$8,312($11,063)	$12,244($11,630)	$11,882($11,355)
2nd year	$8,359($12,452)	$15,280($21,743)	$17,199($15,188)	$14,900($13,052)
3rd year	$8,961($13,234)	$14,682($17,759)	$16,664($13,739)	$12,194($11,280)
Early biological users (top-down strategy):				
1st year	$16,755($15,219)	$21,446($14,770)	$19,584($14,914)	$15,498($14,124)
2nd year	$14,718($17,347)	$18,241($15,415)	$19,938($17,525)	$16,149($16,477)
3rd year	$12,430($17,876)	$15,655($15,516)	$18,402($16,816)	$16,927($17,598)

Mean and standard deviation, in parentheses, were calculated after adjusting to 2010 US$.
Costs incurred in a partial year were annualized.

Table 6.3 Budget Impact Analysis Results

Year	Analysis	Top-down Biological User	Bottom-up Biological User	Difference
1st year	Base-case Analysis	$18,166	$8,945	$9,221
	Sensitivity Analysis	$18,135	$8,900	$9,235 (CI: $9,027 - $9,443)
2nd year	Base-case Analysis	$17,109	$15,038	$2,071
	Sensitivity Analysis	$17,097	$15,033	$2,064 (CI: $1,951 - $2,178)
3rd year	Base-case Analysis	$15,752	$14,268	$1,484
	Sensitivity Analysis	$15,792	$14,316	$1,476 (CI: $1,355 - $1,597)

Sensitivity analysis results were based on the Monte Carlo simulation with 2000 iteration trials.

APPDENDIX

Appendix Table 6.1 Crohn's Disease Severity Classification Criteria

Disease Severity	Claims for Classification*	Coding details (CPT, ICD-9, and HCPCS)
Severe/Fulminant	Hospitalization admission CD diagnosis;	Primary diagnosis: 555.x
	Diagnosis: obstruction, acute suppuration, perforation, refractory disease;	Obstruction: 537.3, 560, 560.8, 560.81, 560.89, 560.9, 574.11, 997.4 Acute suppuration: 461.x, 473.x Perforation: 530.4, 531.1, 532.1, 533.1, 534.1
	Procedures: hyperalimentation;	Hyperalimentation: 278.8, 783.6
	CD related procedures: surgical resection, stricturoplasty, colectormy ileostomy;	Surgical resection: 44202, 44203, 45.51, 45.61, 45.62, 45.71, 46.02, 46.04, 48.4, 48.41, 48.49, 48.5, 48.6, 48.62, 48.63, 48.64, 48.65 Stricturoplasty: 44615 Colectomy: 45.x, 44140, 44141, 44143, 44144, 44145, 44146, 44147, 44150, 44151, 44152, 44153, 44155, 44156, 44160, 44204, 44205, 44206, 44207, 44208, 44210, 44211, 44212 Ileostomy: V44.2, V55.2, 44310, 44312, 44314, 44316, 45136 Colectomy/Eleoctomy: 46.x, v44.4, v44.3
	Rx drugs: immunosuppressant, IV steroid	Generic drug names: cyclosporine, tacrolimus Cyclosporine: J7502, J7503, K0121, K0122, C9438, K0418, 80158, J7515, J7516 Tacrolimus: 80197, J7507, J7508, J7525, C9006 IV steroid: J7506
Moderate-severe	Diagnosis: fistulas, abdominal mass, haemorrhage;	Fistula: 565.1, 569.69, 569.81, 575.5, 576.4, 685.x Abdominal mass: 789.3 Hemorrhage: 530.7, 530.82, 537.83, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578, 578.9, 772.4
	Procedures: abscess drainage;	Abscess/abscess drainage: 75989, 47010, 47011, 49.01, 54.19, 54.91, 55.12

(To be continued)

Disease Severity	Claims for Classification*	Coding details (CPT, ICD-9, and HCPCS)
Moderate-severe	Rx drugs: aTNF (>2 doses), Prednisone, azathioprine, mercaptopurine, methotrexate;	Prednisone: J7506 J7510 K0125 Methotrexate: J8610 J9250 J9260 Mercaptopurine: S0108 Azathioprine: J7500 J7501 K0119 K0120 Anti-TNF: J1745, J0135, J0718, C9249 Generic Drug names: azathioprine, methotrexate, mercaptopurine, infliximab, adalimumab, natalizumab, certolizumab pegol
	Symptoms: high fever, significant weight loss, abdominal pain/tenderness, anaemia	Abdominal pain/tenderness: 789.0, 789.6 Fever: 780.6 Anemia: 280.x, 281.x, 283.x, 285.x, V78.0, V78.1 Nausea/vomitting: 536.2, 564.3, 787.0, 787.01, 787.02, 787.03 weight loss: 783.2
Mild-Moderate	Rx drugs: mesalazine, sulfasalzine, metronidazole, ciprofloxaxin, budesonide, rifaximin, and aTNF (1 dose only)	Generic Drug names: mesalazine, sulfasalzine, metronidazole, ciprofloxaxin, budesonide, rifaximin, infliximab, adalimumab, natalizumab, certolizumab pegol HCPCS codes: J1745, J0135, J0718, C9249, J7506, J7510, K0125, J8610, J9250, J9260, S0108, J7500, J7501, K0119, K0120
Remission	Does not meet criteria for severe/fulminant, Moderate-severe, and Mild-moderate	

* Source: Malone et al. 2010

Appendix Table 6.2 Parameters for Sensitivity Analysis

Parameter	Base-case value	Distribution	Specification
Probability of a CD patient assessed with different disease severity in the 1st year after diagnosis	Remission: 0.236 Mild-mod.: 0.117 Mod.-sev.: 0.410 Sev./Fulm.: 0.237	Dirichlet	Dirichlet(236;117;410;237)
Prescription drug cost of a late biological user with different disease severity in the 1st year	Remission: $579 Mild-mod.: $8,312 Mod.-sev.: $12,244 Sev./Fulm.: $11,882	Gamma(κ, θ)	κ =0.028, θ=20,413 κ =0.565, θ=14,723 κ =1.108, θ=11,047 κ =1.095, θ=10,852
Prescription drug cost of a late biological user with different disease severity in the 2nd year	Remission: $8,359 Mild-mod.: $15,280 Mod.-sev.: $17,198 Sev./Fulm.: $14,900	Gamma(κ, θ)	κ =0.451, θ=18,549 κ =0.494, θ=30,938 κ =1.282, θ=13,413 κ =1.303, θ=11,433
Transition probability of a late biological user with remission disease in the 1st year to different disease severity in the 2nd year	Remission: 0.265 Mild-mod.: 0.139 Mod.-sev.: 0.390 Sev./Fulm.: 0.206	Dirichlet	Dirichlet(265;139;390;206)
Transition probability of a late biological user with mild disease in the 1st year to different disease severity in the 2nd year	Remission: 0.171 Mild-mod.: 0.370 Mod.-sev.: 0.288 Sev./Fulm.: 0.171	Dirichlet	Dirichlet(171;370;288;171)
Transition probability of a late biological user with moderate disease in the 1st year to different disease severity in the 2nd year	Remission: 0.112 Mild-mod.: 0.077 Mod.-sev.: 0.639 Sev./Fulm.: 0.172	Dirichlet	Dirichlet(112;77;639;172)
Transition probability of a late biological user with severe disease in the 1st year to different disease severity in the 2nd year	Remission: 0.129 Mild-mod.: 0.123 Mod.-sev.: 0.366 Sev./Fulm.: 0.382	Dirichlet	Dirichlet(129;123;366;382)
Prescription drug cost of a early biological user with different disease severity in the 1st year	Remission: $16,755 Mild-mod.: $21,456 Mod.-sev.: $19,584 Sev./Fulm.: $15,498	Gamma(κ, θ)	κ =1.212, θ=13,823 κ =2.108, θ=10,172 κ =1.724, θ=11,357 κ =1.204, θ=12,871
Prescription drug cost of a early biological user with different disease severity in the 2nd year	Remission: $14,718 Mild-mod.: $18,241 Mod.-sev.: $19,938 Sev./Fulm.: $16,150	Gamma(κ, θ)	κ =0.720, θ=20,446 κ =1.400, θ=13,027 κ =1.294, θ=15,405 κ =0.961, θ=16,811

Parameter	Base-case value	Distribution	Specification
Transition probability of a early biological user with remission disease in the 1st year to different disease severity in the 2nd year	Remission: 0.690 Mild-mod.: 0.054 Mod.-sev.: 0.151 Sev./Fulm.: 0.105	Dirichlet	Dirichlet(690;54;151;105)
Transition probability of a early biological user with mild disease in the 1st year to different disease severity in the 2nd year	Remission: 0.289 Mild-mod.: 0.386 Mod.-sev.: 0.228 Sev./Fulm.: 0.097	Dirichlet	Dirichlet(289;386;228;97)
Transition probability of a early biological user with moderate disease in the 1st year to different disease severity in the 2nd year	Remission: 0.250 Mild-mod.: 0.074 Mod.-sev.: 0.549 Sev./Fulm.: 0.127	Dirichlet	Dirichlet(250;74;549;127)
Transition probability of a early biological user with severe disease in the 1st year to different disease severity s in the 2nd year	Remission: 0.297 Mild-mod.: 0.054 Mod.-sev.: 0.210 Sev./Fulm.: 0.439	Dirichlet	Dirichlet(297;54;210;439)

1.Parameters for Gamma distributions are approximated by mean and standard deviation: $\kappa = \bar{u}^2/s^2$, $\theta = s^2/\bar{u}$
2.Prescription drug costs in the 3rd year and transition probability from the 2nd to the 3rd year for both early and late biological users are similarly specified with Gamma and Dirichlet distributions. Detailed specifications for each parameter are not included in the table above.

Appendix Table 6.3 Prescription Drug Costs by Biological Drug by Claim Type

Claim Type	2005	2006	2007	2008	2009
Biologics for intravenous use, including infliximab and natalizumab					
Medical benefit	$6,152,045	$24,247,237	$28,131,469	$44,929,533	$43,858,861
Pharmacy benefit	$342,871	$670,609	$581,837	$1,285,359	$1,258,710
Biologics for subcutaneous use, including adalimumab and certolizumab pegol					
Medical benefit	n/a	$18,610	$165,289	$731,150	$553,299
Pharmacy benefit	n/a	$370,813	$3,504,359	$16,057,968	$22,656,426

Prescription drug costs under pharmacy benefit are the total costs of the claims with the following NDC numbers: 57894003001for infliximab; 50474070062, 50474071079, and 50474071081 for certolizumab pegol; 00074379901, 00074379902, 00074433902, 00074433906, 00074433907, 00074937402, 54569552400, 54868482200 for adalimumab; 59075073015 for natalizumab.
Prescription drug costs under medical benefit are the total costs of the claims with the following HCPCS codes: J1745 for infliximab; J0135 for Adalimumab; J2323 for natalizumab; J0718 and C9249 for certolizumab pegol.
All prescription costs were adjusting to 2010 US$.

Appendix Table 6.4 Comparison of Prescription Drug Costs of Non-biological Drugs

Year	Analysis	Top-down Biological User	Bottom-up Biological User	Difference
1st year	Base-case Analysis	$1,073	$2,239	$1,166
	Sensitivity Analysis	$1,078	$2,252	$1,175 (CI: $1,147 - $1,202)
2nd year	Base-case Analysis	$1,124	$2,597	$1,473
	Sensitivity Analysis	$1,106	$2,571	$1,465 (CI: $1,425 - $1,505)
3rd year	Base-case Analysis	$1,113	$2,677	$1,564
	Sensitivity Analysis	$1,120	$2,646	$1,526 (CI: $1,493 - $1,560)

Sensitivity analysis results were based on Monte Carlo simulation with 2000 iteration trials.

Appendix Table 6.5 Case Scenario Sensitivity Analysis Results

Year	Analysis	Top-down Biological User	Bottom-up Biological User	Difference
Case Scenario 1: Probabilities in the first year were based on late users' data in previous years				
1st year	Base-case Analysis	$18,634	$10,967	$7,667
	Sensitivity Analysis	$18,736	$11,016	$7,720 (CI: $7,567 - $7,873)
2nd year	Base-case Analysis	$17,442	$15,227	$2,215
	Sensitivity Analysis	$17,441	$15,244	$2,197 (CI: $2,096 - $2,299)
3rd year	Base-case Analysis	$15,932	$14,317	$1,615
	Sensitivity Analysis	$15,916	$14,310	$1,606 (CI: $1,490 - $1,722)
Case Scenario 2: Probabilities in the first year were based on early users' data in previous years				
1st year	Base-case Analysis	$17,711	$6,966	$10,745
	Sensitivity Analysis	$17,712	$6,944	$10,768(CI:$10,542-$10,994)
2nd year	Base-case Analysis	$16,785	$14,854	$1,931
	Sensitivity Analysis	$16,751	$14,777	$1,974 (CI: $1,849 - $2,099)
3rd year	Base-case Analysis	$15,576	$14,220	$1,356
	Sensitivity Analysis	$15,607	$14,137	$1,470 (CI: $1,344 - $1,596)

Sensitivity analysis results were based on the Monte Carlo simulation with 2000 iteration trials.

CHAPTER VII:

EARLY ADOPTION OF BIOLOGICAL THERAPIES BY PATIENTS WITH CROHN'S DISEASE: COST ANALYSIS FROM THIRD PARTY PAYERS' PERSPECTIVE

Background: As more patients with Crohn's disease (CD) adopt biological therapies early in their disease course, the economic impact of this treatment strategy on third party payers becomes increasingly important.

Objectives: This study sought to evaluate whether or not the top-down treatment approach is cost-saving for payers when considering potential improvements in spending for non-prescription healthcare services.

Methods: A decision tree model was constructed to compare total healthcare costs for biological therapy users during the first three years following a CD diagnosis when using two different treatment strategies, top-down and bottom-up approach. Parameters for the decision model, including transition probabilities and healthcare costs, were derived from cohort analyses based on claims data from CD patients who used biological therapies early or late in their disease course. Study cohorts were selected from the MarketScan Commercial Claims and Encounter database from 2005 to 2009.

Results: Total healthcare costs were predicted at $33,025 in the first year for CD patients who used top-down treatment approach, which was $9,073 (CI: $8,716-$9,429) more than the costs for bottom-up therapy users. The difference in total healthcare costs decreased to $1,299 (CI: $1,005-$1,593) in the second year, and further reduced to $900 (CI: $660-$1,140)

in the third year. The cost neutrality between the two treatment strategies for CD management was primarily attributed to the cost reduction for both inpatient and outpatient services. A sub-group analysis on CD patients who used biological therapies more frequently in the three months after their initial dose demonstrated a saving of $564 (CI: $268-$862) in healthcare costs in the third year of disease if the top-down strategy was used.

Conclusion: Compared to conventional bottom-up therapy, the top-down treatment approach is cost neutral, and potentially cost saving for payers. It is recommended that payers balance the short-term burden of increased drug costs and long-term gain of savings from total healthcare services when evaluating their health plans.

7.1 Introduction

Crohn's disease (CD) is a major inflammatory bowel disease (IBD) that affects the gastrointestinal tract with symptoms of diarrhea, abdominal pain, fatigue, fever, bowel obstruction, and passage of blood and mucus.[1] CD substantially impairs quality of life for patients and entails great financial burden to the US society.[2] In 2006, total direct medical costs were estimated at $18,000 per patient and over $10 billion to the US healthcare system.[3] Medical costs for Crohn's disease may have increased even more in recent years because novel biological therapies were more frequently prescribed to CD patients.

Four biological agents (including infliximab, adalimumab, natalizumab and certolizumab pegol) have been approved by the FDA to treat CD. Compared to conventional drug therapies, these biological therapies have many therapeutic benefits, including a higher response rate, more rapid onset of clinical response, greater effectiveness in maintaining

long-term remission, and significant improvement in health related quality of life.[7-9] As a result, the treatment strategy for CD is currently shifting toward the adoption of biological therapy as a first-line treatment regimen. Conventionally, biological therapies were reserved as the last medical resort for patients who are refractory or intolerant to conventional drugs, which include aminosalicylates, antibiotics, steroids, and immunomodulators. This strategy, referred to as 'bottom-up' therapy, advocates that patients start with less expensive drugs, and gradually move to more advanced biological therapies. Recently, clinical studies have shown that biological therapies result in a more rapid remission and higher remission rate if they are introduced into the treatment algorithm early in the disease course.[12, 13] Thus, a new treatment regimen, known as the 'top-down' approach, suggests that patients start with biological therapy as first-line treatment, either in combination with immunomodulators or as mono therapy.

The adoption of biological therapy as a first line treatment can significantly increase medication costs. However, if these medications are proven to be more effective, they may result in lower health care spending for other services. This study takes an important step in the effort to conduct effectiveness research on biological therapies by comparing healthcare costs that incurred by CD patients who use either the top-down or bottom-up approach when adopting novel biological therapies into treatment regimen. More specifically, we aim to determine costs that are paid by managed care organizations (MCOs) for all health care services utilized by CD patients, including inpatient, outpatient, and emergency department services as well as prescription drugs. In this study, the targeted population is patients who are commercially insured. This population is thought to be representative of the majority of Crohn's disease patients as this condition is most common in people of working age who

often obtain health insurance through their employer.[90] In the private sector of the US healthcare system, more than 95% of insured persons are enrolled in MCOs, who not only manage the use of healthcare services, but control their costs. Increasing healthcare expenditures in recent years can be partly attributed to the adoption of novel technologies and therapies.[91] Biological therapies for CD treatment provide unprecedented medical benefits to patients, however, they also impose a substantial financial burden to payers because they cost five to ten times more than conventional drugs.[3, 74] In a previous unpublished study, we showed that the annual drug cost for biological users was $16,848 which is significantly higher than drug costs for non-biological users which averaged $2,919 (see Chapter 6).

Increasing prescription drug spending leads to heightened awareness of medication expenditures by managed care organizations (MCOs) charged with managing drug costs. MCOs have a number of cost-containment strategies available, including prior authorization, quantity limits, and care management.[92] A thorough understanding of medication and health expenditures resulting from the shift in prescribing from the bottom-up to top-down approach would help inform MCO's about the potential benefits that might result from increasing prescription expenditures for biological treatments.

As with all medication treatments, the benefits from treatment are only achieved in patients who use medication appropriately. For conventional small-molecule drugs, medication adherence plays an important role in optimizing their treatment effect.[93] Literature about adherence to biological therapies, however, is scarce due to technical barriers in measuring and calculating medication adherence and persistence, including diverse administration methods (i.e., intravenous infusion and subcutaneous injection) and different distribution channels (i.e., physician office visit and pharmacy retail).[94] For

biological therapies, discontinuation rate and dose frequency are commonly used as crude adherence measurements. Among CD patients treated with infliximab, 68% of them discontinued treatment twelve months following initiation, and up to 80% discontinued infliximab after thirty-six months.[40] This high treatment discontinuation rate was also observed among patients with rheumatoid arthritis.[95] Evidently, CD patients with more frequent use of infliximab as maintenance therapy in the first year had a lower rate of hospitalization and increased medical costs.[44]

In this study, a decision analytical model is employed to predict the cost difference to MCOs when the CD treatment strategy changes from the conservative bottom-up to aggressive top-down approach. We further evaluate the economic impact of this treatment strategy change on a subgroup of CD patients who used biological therapies more persistently to examine the role of patient adherence on health care costs. The results from this study will enrich the literature with information regarding potential reductions in healthcare costs for CD patients from the adoption of a shift in treatment strategy from late to early adoption.

7.2 Methods

Sample Selection

The study sample was selected from the MarketScan Commercial Claims and Encounter (CCAE) database (Thomson Reuters, Ann Arbor, Michigan). These data comprised of data from January 1, 2005 to December 31, 2009. Patients were eligible for inclusion in our study sample if they met the following criteria: a) a confirmed diagnosis of Crohn's disease; b) age between 18 and 64; c) enrollment in an MCO; d) a minimum of one

year of continuous enrollment after CD diagnosis; e) a 6-month, disease free period before the first CD treatment; and f) at least one infusion/injection of an FDA-approved biological therapy (namely, infliximab, adalimumab, natalizumab, certolizumab pegol). Given the potential for these medications to be used for other FDA approved conditions, patients were excluded from the study sample if they were also diagnosed with ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and juvenile idiopathic arthritis. In total 6,068 patients were identified as eligible biological users for this study. Among them, 3,082 patients initiated biological therapy as their initial treatment for Crohn's disease. These patients were categorized as early adoption biological users, and considered as top-down therapy users. The remaining patients (n=2,986), who used other CD treatments (aminosalicylates, corticosteroids, antibiotics, and immunomodulators) prior to biological therapies, were defined as late adoption biological users, and deemed as bottom-up therapy users. While early adopters started to use biological therapies three months on average after CD diagnosis, late adopters waited twelve months to initiate biological treatment.

Decision Modeling

A decision tree was developed to compare total healthcare costs for CD patients who followed top-down or bottom-up treatment approaches for biological therapies (see Figure 6.1). A three-year time frame was built into the model to predict annual healthcare costs following the initial diagnosis of CD. Disease severity was assessed using a claims based algorithm developed by Malone et al.[68] According to patients' healthcare utilization records in each year, disease severity was classified into one of four categories: a) remission; b) mild to moderate; c) moderate to severe; or d) severe or fulminant (See Appendix Table

6.1 for detailed classification criteria for each severity category). Initial pathways depicted on the decision tree for each treatment strategy show disease severity in the first year following CD diagnosis. Disease severity for CD patients was either changed, or remained the same, from the first year to the second year. A transition in disease severity from the first year to the second year is demonstrated by the pathways in the second layer of the decision tree. To populate the decision model, cohort analyses were conducted to estimate healthcare costs (payoff value) and the transition probabilities for all pathways. Under the top-down scenario, the probability of severity allocation and cost assignment of each classification of severity were based on the estimation from patients who adopted biological therapies in their initial CD treatment in a large claims database from 2005 to 2009. For patients under the bottom-up scenario, their model parameters were estimated from patients who used biological therapies later than conventional drugs in the same database. Algorithms for disease severity classification and transition probability calculation were described in another study (see Chapter VI for details).

Healthcare Costs

Total healthcare costs were of primary interest in this study. For CD patients who used top-down or bottom-up treatment strategy, total healthcare costs were comprised as the sum of costs for four individual healthcare services, including inpatient, outpatient, emergency department services and prescription drugs. In each year following the diagnosis of CD, healthcare costs were estimated based on claims from 2005 to 2009. Annual healthcare costs were the average amount that payers reimbursed patients for all healthcare services, including prescription drugs, in each 12-month period following the CD diagnosis.

Healthcare costs occurring in each calendar year were adjusted to the value of the U.S. dollar in 2010, then calculated annually according to patients' treatment strategy and disease severity classification (see Table 7.1). In addition, the costs for each of the four individual healthcare services (e.g., inpatient services) were similarly estimated based on claims data for each specific service area (see Appendix Table 7.1).

In the cost summarization for total healthcare or individual healthcare services, only patients with a full year of enrollment in MCOs were included. In the first year of disease, all eligible patients automatically had a one-year enrollment period as required by the previously defined inclusion criteria. Patients who were partially enrolled in MCOs were not taken into consideration when calculating the annual healthcare costs for the second and third year. For example, if a patient had continuous enrollment for 27 months (2 years and 3 months) following CD diagnosis, then this patient was only eligible for cost summarizations in the first and second years.

Examining the distribution of health care costs, we found a small number of patients with outlier expenditures for inpatient services. Among CD patients eligible for cost summarization (6,068 in the first, 3,825 in the second and 1,878 in the third year of CD), 17 patients in one of three years, or 0.1% of 11,771 patient-years, incurred annual inpatient costs exceeding $250,000 per year. A review of claims data showed that these high inpatient costs were attributable to lengthy inpatient stays and non-CD related therapies or procedures (e.g., chemotherapy for cancer treatment). To account for potential inflation of our cost estimates on the basis of these outlier observations, we truncated inpatient costs at $250,000. Examining annual costs for other healthcare services, i.e., outpatient, emergency department services, and prescription drugs did not reveal concerns regarding outlier observations.

Base Case Analysis

The base case in the decision model refers to a new Crohn's disease patient who uses biological therapies following the conventional 'bottom-up' strategy. The alternative case is the patient who instead uses biological therapies following the new 'top-down' approach. Regardless of case scenario, the patient was assumed to have the same severity of disease as an average biological user had during the first year of disease from 2005 to 2009. Total healthcare costs were estimated accordingly by disease severity and treatment strategy adapted during the disease course. In the second and third year of disease, patients were allocated transition probabilities for different disease severities. Base case analysis compared total healthcare costs of the base case patient with the alternative case patient in the first three years of disease. The difference in total healthcare costs demonstrates the economic effect of new top-down treatment strategy.

Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) using Monte Carlo simulation was performed to estimate the impact of uncertainty regarding input parameters in the decision model. The input parameters, both transition probabilities and healthcare costs, were each specified with different distributions. Given the complexity of multiple categories for disease severity, the Dirichlet distribution was used to represent the combination of multinomial parameter probabilities. Although a series of conditional beta distributions could describe multinomial data, the Dirichlet distribution has been successfully implemented to ease in fitting multinomial probabilities in decision modeling.[71] For healthcare costs, a gamma

distribution was used to describe its distribution given that costs are constrained on the interval 0 to positive infinity (see Appendix Table 7.3).

Probabilistic sensitivity analysis (PSA) using the Monte Carlo simulation was performed to quantify the impact of input parameters on the uncertainty in model output. Both base case and sensitivity analyses were conducted in TreeAge Pro 2011 (TreeAge Software Inc., Williamstown, MA). The study was approved by the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill.

Subgroup Analysis

From the study sample (n=6,608 CD patients), more persistent biological users were selected for a subgroup analysis. The recommended dosage to treat CD in the first three months (12 weeks) are: a) for infliximab, 3 infusions at weeks 0, 2, 6; b) for adalimumab, 7 injections on days 1, 15, 29, weeks 6, 8, 10, and 12; c) for natalizumab, 4 infusions at weeks 0, 4, 8, and 12; and d) for certolizumab pegol, 5 injections at weeks 0, 2, 4, 8, and 12. In this study, we used the number of doses of biological therapies as the crude measurement of drug adherence. Patients who used three or more doses of biological therapies (including the initial dose) during the three months following their initial dose were identified as frequent biological users. There were 2,404 (39.6% of 6,068) patients who were eligible for the subgroup analysis. Their characteristics, including age, gender, and comorbidity, were similar to both early and late biological users (see Appendix Table 7.6).

Total healthcare costs for the subgroup of CD patients were compared by using the same decision tree model for base case and sensitivity analyses above (see Figure 6.1). Frequent biological users in the subgroup were categorized as early frequent biological users

(n=848, or 27.5% of 3,082) if biological therapy was included in their initial treatment, or as late frequent biological users (n=1,556, or 52.1% of 2,986) if biological therapies were used later in their disease course after other conventional treatments were attempted. We considered early frequent biological users followed top-down treatment strategy, and late frequent biological users used bottom-up therapy approach. According to the treatment strategy of adopting biological therapy and annual assessment of disease severity, total healthcare costs and transition probabilities in the first three years of CD for frequent biological users were calculated based on their claims data in previous years (see Appendix Tables 7.4 and 7.5).

7.3 Results

Base Case Analysis

In the first year of CD, total healthcare costs were estimated at $32,910 for patients who followed top-down treatment approach and $23,706 if they used bottom-up approach. This difference was mainly explained by the costs of biological therapies incurred to CD patients. On average, biological therapies were initiated 89 days after diagnosis if patients followed top-down strategy to adopt these expensive therapies early, and 365 days if patients used the bottom-up approach. The top-down treatment strategy is associated with 38.8% higher total healthcare costs than bottom-up approach. Total healthcare costs in the second and third years were predicted at $28,500 and $26,384, respectively, if patients used the top-down approach. These predicted values are only 4.2% (second year) and 3.2% (third year) higher than those for patients using bottom-up approach (see Table 7.2).

For each of the three years following CD diagnosis, the costs of inpatient services were $5,672 (first year), $4,148 (second year), and $4,293(third year) for patients that used the top-down strategy. Inpatient service costs were $6,148, $5,387 and $4,941 for patients using the bottom-up therapy in the first, second and third years, respectively. Outpatient service costs were $8,498 for top-down users in the first year of CD, about 6% higher than costs for bottom-up users. However, costs of outpatient services for top-down users were 9% and 6% lower than bottom-up users in the second and third year of disease, respectively. Prescription drug costs incurred by top-down users were $18,166, twice as much as costs for bottom-up users ($8,945) in the first year. Prescription drug costs for bottom-up users increased to $13,371 in the second year and remained elevated in the third year ($12,895) of CD, the differences in prescription drug costs of patients using two different strategies became smaller, even though the costs for top-down users remained 20% (second year) and 16% (third year) higher. Compared to costs for other healthcare services, emergency room services only contributed a small fraction of the total health care costs, totaling $574, $478, and $388 for top-down users in the first, second, and third years following CD diagnosis (see Figure 7.1 and Appendix Table 7.2).

Sensitivity Analysis

Results of the probabilistic sensitivity analysis confirmed findings that informed the base case analysis. The incremental costs of total healthcare services from top-down treatment startegy rapidly decreased from $9,073 (95% confidence interval: $8,716-$9,429) to $1,299 (CI: $1,005-$1,593) from the first year to the second year, and to $900 (CI: $660-$1,140) in the third year. (see Table 7.2). The differences in the costs of inpatient, outpatient,

ER services and prescription drugs between the two user groups were statistically significant and consistent with the findings from base case analyses (see Appendix Table 7.2).

Subgroup Analysis

Total healthcare costs for early and late biological users with greater persistence during the first three months of treatment were $34,613 and $23,435, respectively, in the first year of CD. Total healthcare costs for patients following two treatment strategies became comparable at $29,940 (early) and $29,043 (late) in the second year. In the third year, total healthcare costs for top-down users continuously decreased to $26,601, which was $690 lower than costs for bottom-up biological users ($27,291). Sensitivity analyses demonstrated that the cost-saving of $690 from top-down approach was statistically significant.

7.4 Discussion

This is the first study using large, real-world data to evaluate the long term economic outcomes of biological therapies used by CD patients following different treatment strategies. Top-down treatment approach demonstrated cost neutrality for payers after the first year of disease. Although healthcare costs for patients who follow top-down therapy in the first year were elevated substantially, their costs became comparable with those using the bottom-up approach in the second and third year of CD. This study has demonstrated for the first time that the top-down treatment approach can be cost neutral in the long term when compared to the conventional bottom-up treatment strategy that recommends to reserve biological therapy as last medical resort.

The subgroup analyses further showed that top-down treatment strategy can be cost-saving among CD patients who used biological therapies more aggressively and persistently after the initial dose of biological therapy. This suggests that better compliance to biological therapies can result in improved economic outcomes, specifically, reduced healthcare costs for third party payers. In recent years, payers have been aggressively making efforts to contain healthcare costs, especially expenses related to innovative technology and medications.[14, 92] The results from our study provide important information to payers regarding the long-term value of new biological therapies for Crohn's disease. Our results suggest that formulary restrictions for biological treatments in CD patients may not yield cost savings and should be considered carefully. More persistent use of biological therapies among CD patients should be encouraged to improve adherence, resulting in better clinical and economic outcomes.

Total healthcare services were grouped into the following four categories: a) inpatient services, including facility and physician services; b) outpatient services, rendered in a doctor's office, hospital outpatient facility, or other outpatient facility; c) emergency room services; and d) prescription drugs, including biological therapies and conventional medications for CD treatment. As shown in Figure 7.1, total healthcare costs for patients using top-down therapy were substantially higher in the first year of disease, and became convergent thereafter. In the second and third years, top-down therapy incurred lower costs for inpatient, outpatient, and ER services, although drug costs remained higher than those for bottom-up therapy users. This indicates that potential cost-savings from top-down treatment strategy can be attributed mainly to the decreased cost of non-drug services (i.e., inpatient, outpatient and ER services).

When a decision tree model was employed to rigorously predict total healthcare costs for patients who use top-down and bottom-up treatment strategy of biological therapies, we derived all cost parameters and transition probabilities from CD patients in a large claims database. This approach for real world data modeling is accompanied by some challenges due to imperfection of data. We noticed that there were 17 cases, or 0.1% of 11,771 in total, with very high annual costs (more than $250,000 per year) for inpatient services. For example, the highest inpatient expenditures for one patient exceeded $1 million. These outliers could significantly distort the cost distribution by elevating the mean and standard deviation of certain patient groups when stratified by disease severity (see Appendix Table 7.7). To avoid the disproportionate influence from these cost outliers, a truncation method was applied prior to obtaining cost parameters by substituting extremely high inpatient costs with a fixed value of $250,000. Additional decision analyses based on both unadjusted costs and adjusted costs with a truncation value of $500,000 showed that these outliers with high inpatient service costs inflated the predicted costs for total healthcare, particularly in the third year of disease (see Appendix Table 7.8). Because it is not possible to verify all claims pertaining to high outlier inpatient costs, the accuracy of claims data can be a potential limitation in this study powered by real-world data.

A lack of patient-level clinical and medical information in the claims database introduces another limitation. In order to obtain severity of disease in this study, we used an empirical method developed by Malone et al. to classify patients into four different severity categories by using patients' medical and pharmacy claims.[68] This method used healthcare utilization to approximate disease severity, and could be inaccurate for patients who under- or over-utilized healthcare services. Inadequate information about the medical cause of

claims prevented us from separating CD-related claims from all claims related to other medical causes, even though the diagnosis codes (e.g., ICD-9) were provided in the claims database. Additionally, the diagnosis codes were not consistently available across all services in a uniform code system. Therefore, it is not practical to differentiate claims by diagnosis codes, even though it would be theoretically meaningful to use the difference in CD-related healthcare costs to represent the economic outcomes of biological therapies when adopted by patients under a different treatment strategy.

We assumed that patients have equal preference for different treatment strategies. Their choices of either early or late adoption of biological therapies into their treatment regimen was not affected by patients' characteristics, health status, insurance coverage, and comorbid conditions. In a previous unpublished study (see Chapter 5), we did not find a significant difference in demographic characteristics (e.g., age and gender) when comparing early and late biological users in a large claims database. However we noticed that early biological users appeared to have fewer comorbid conditions, used fewer prescriptions in six months prior to diagnosis, and were more likely to be working for smaller employers (see Table 5.1). This suggests that other factors, such as employment and health insurance coverage, could impact a given patient's treatment strategy and resulting economic outcomes. This study provided more general information about the economic outcomes for patients enrolled in any MCOs. Further research can be conducted on patients enrolled in specific health plans to provide more customized information of interest to plan administrators.

Additionally, long-term side effects of biological therapies were not modeled in this three-year study due to lack of long-term safety data. Biological therapies are generally well tolerated among CD patient, however, adverse events, including infections, infusion reactions,

lymphomas, and demyelinating disease, were reported in clinical studies.[96] Some long-term side effects, e.g., reactivation of tuberculosis, may have not been captured in the claims database. These side effects may undermine clinical benefit of biological therapy, and incur extra medical costs. Therefore, long-term healthcare costs may be underestimated for CD patients who use biological therapies in their treatment algorithm.

7.5 Summary

For patients with Crohn's disease, new top-down treatment strategy for biological therapy showed a long-term cost-neutrality to Managed Care Organizations (MCOs) when compared to conventional bottom-up approach. CD patients who used biological therapies more frequently after their initial dose showed that cost savings can be achieved as early as the third year after CD diagnosis. The rapid decrease in the incremental costs of total healthcare services from the top-down treatment approach was attributed mainly to the reduction of costs for non-drug services. This study is the first to demonstrate the long term value of biological therapies for CD treatment, and improved economic outcomes when adopted early in the initial treatment.

Figure 7.1 Comparison of Healthcare Costs of Individual Services

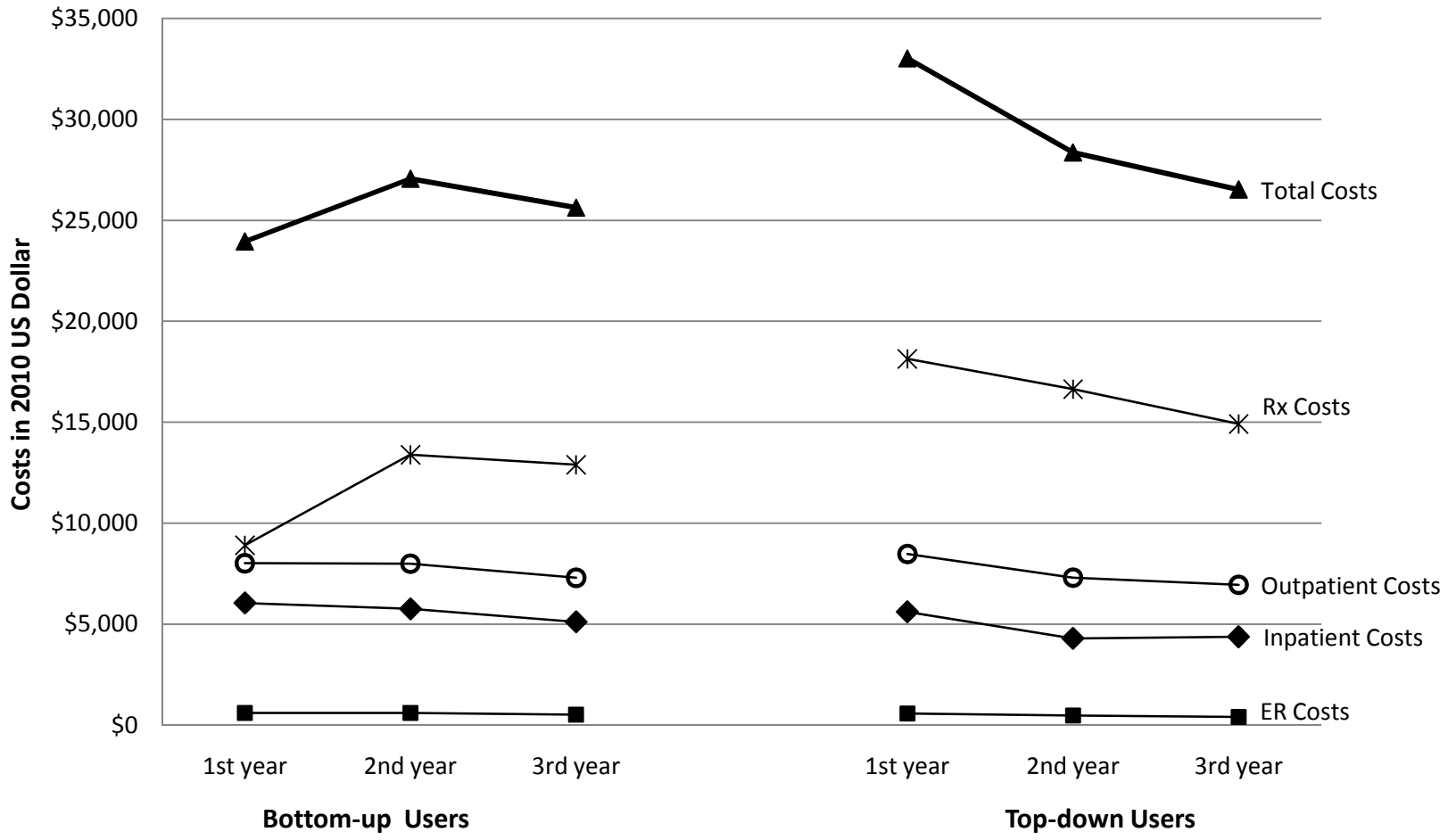


Table 7.1 Total Healthcare Costs by Disease Severity

Year/Severity	Remission	Mild-moderate	Moderate-severe	Severe/Fulminant
Late biological users(N=2,986)**:**				
1st year	$6,415($10,655)	$16,416($17,936)	$23,336($21,708)	$45,162($40,116)
2nd year	$10,660($15,102)	$21,362($26,589)	$25,659($20,010)	$46,864($44,390)
3rd year	$13,568($17,010)	$20,668($23,703)	$24,879($20,544)	$39,857($37,627)
Early biological users (N=3,082):				
1st year	$24,904($20,080)	$29,467($18,360)	$30,100($22,205)	$47,444($46,555)
2nd year	$20,389($18,901)	$24,316($19,344)	$30,051($24,278)	$43,570($40,557)
3rd year	$15,383($16,658)	$22,720($18,443)	$27,875($26,350)	$46,189($43,666)

Mean and standard deviation, in parentheses, were calculated after adjusting to 2010 US$.
Only costs incurred in a full year were summarized.

Table 7.2 Comparison of Total Healthcare Costs Between Top-down and Bottom-up Users

Year	Analysis	Top-down Biological User	Bottom-up Biological User	Difference
1st year	Base-case Analysis	$32,910	$23,706	$9,204
	Sensitivity Analysis	$33,025	$23,952	$9,073 (CI: $8,716 - $9,429)
2nd year	Base-case Analysis	$28,500	$27,362	$1,138
	Sensitivity Analysis	$28,362	$27,063	$1,299 (CI: $1,005 - $1,593)
3rd year	Base-case Analysis	$26,384	$25,563	$821
	Sensitivity Analysis	$26,530	$25,630	$900 (CI: $660 - $1,140)

Sensitivity analysis results were based on the Monte Carlo simulation with 2000 iteration trials.

Table 7.3 Subgroup Analysis Results of Total Healthcare Costs for Frequent Biological Users*

Year	Analysis	Top-down Biological User	Bottom-up Biological User	Difference
1st year	Base-case Analysis	$34,613	$23,435	$11,178
	Sensitivity Analysis	$34,585	$23,361	$11,224(CI:$10,850-$11,598)
2nd year	Base-case Analysis	$29,940	$29,043	$897
	Sensitivity Analysis	$29,931	$29,184	$746 (CI: $462 - $1,030)
3rd year	Base-case Analysis	$26,601	$27,291	-$690
	Sensitivity Analysis	$26,689	$27,253	-$564 (CI: -$862 - -$268)

*Frequent biological users for subgroup analysis were CD patients who used 3 or more doses of biological therapies in the first three months following the initial dose (inclusive).
Sensitivity analysis results were based on the Monte Carlo simulation with 2000 iteration trials.

APPDENDIX

Appendix Table 7.1 Healthcare Costs for Individual Services by Disease Severity

Year/Severity	Remission	Mild-moderate	Moderate-severe	Severe/Fulminant
Costs for Inpatient Services				
Late biological users:				
1st year	$1,226($5,045)	$1,006($4,355)	$2,136($11,860)	$20,530($29,297)
2nd year	$161($1,418)	$894($5,332)	$1,807($9,228)	$19,863($32,193)
3rd year	$292($2,437)	$1,855($9,594)	$1,993($11,004)	$17,856($30,142)
Early biological users:				
1st year	$648($3,911)	$306($2,691)	$1,896($7,544)	$19,858($36,220)
2nd year	$550($3,190)	$1,134($7,963)	$2,534($11,074)	$15,481($29,419)
3rd year	$329($1,917)	$1,050($4,150)	$3,132($17,493)	$15,661($29,917)
Costs for Outpatient Services				
Late biological users:				
1st year	$4,477($8,217)	$6,804($12,513)	$8,521($11,964)	$11,241($16,984)
2nd year	$4,407(9,513)	$6,925($11,473)	$7,891($11,582)	$11,497($18,182)
3rd year	$4,815(11,071)	$6,600($12,404)	$7,212($10,722)	$9,557($12,939)
Early biological users:				
1st year	$7,165($12,276)	$7,448($10,643)	$8,172($12,794)	$10,908($15,010)
2nd year	$6,186($10,159)	$5,931($7,711)	$6,893($8,431)	$10,828($12,498)
3rd year	$4,198($8,104)	$5,798($6,470)	$6,660($8,484)	$12,565($18,017)
Costs for Prescription Drugs				
Late biological users:				
1st year	$579($3,438)	$8,312($11,063)	$12,244($11,630)	$11,882($11,355)
2nd year	$5,998($9,945)	$13,298($23,250)	$15,555($12,490)	$13,876($12,329)
3rd year	$8,269($12,326)	$11,904($16,530)	$15,301($13,512)	$11,273($9,780)
Early biological users:				
1st year	$16,755($15,219)	$21,446($14,770)	$19,584($14,914)	$15,498($14,124)
2nd year	$13,288($15,301)	$17,085($14,257)	$20,274($18,399)	$16,182($16,252)
3rd year	$10,749($13,682)	$15,682($16,124)	$17,809($16,752)	$16,724($17,161)
Costs for Emergent Room Services				
Late biological users:				
1st year	$132($413)	$294($976)	$437($1,682)	$1,510($3,564)
2nd year	$95($395)	$245($739)	$406($1,375)	$1,628($4,027)
3rd year	$191($636)	$309($1,087)	$380($1,339)	$1,171($3,063)
Early biological users:				
1st year	$336($2,008)	$267($735)	$448($1,439)	$1,179($2,238)
2nd year	$367($2,746)	$166($476)	$350($1,113)	$1,081($2,688)
3rd year	$107($366)	$191($596)	$274($1,007)	$1,241($3,434)

Mean and standard deviation, in parentheses, were calculated after adjusting to 2010 US$.
Only costs incurred in a full year were summarized.

Appendix Table 7.2 Comparison of Healthcare Costs of Individual Services for Top-down and Bottom-up Biological Users

Year	Analysis	Top-down Biological User	Bottom-up Biological User	Difference
Costs for Inpatient Services				
1st year	Base-case Analysis	$5,672	$6,148	-$476
	Sensitivity Analysis	$5,607	$6,045	-$438 (CI: -$524 - -$352)
2nd year	Base-case Analysis	$4,148	$5,387	-$1,239
	Sensitivity Analysis	$4,289	$5,751	-$1,462(CI: -$1,659 - -$1,264)
3rd year	Base-case Analysis	$4,293	$4,941	-$648
	Sensitivity Analysis	$4,367	$5,106	-$336 (CI: -$484 - -$187)
Costs for Outpatient Services				
1st year	Base-case Analysis	$8,498	$8,011	$487
	Sensitivity Analysis	$8,470	$8,013	$457 (CI: $278 - $636)
2nd year	Base-case Analysis	$7,291	$8,001	-$710
	Sensitivity Analysis	$7,300	$7,987	-$687 (CI: -$750 - -$623)
3rd year	Base-case Analysis	$6,808	$7,229	-$421
	Sensitivity Analysis	$6,948	$7,291	-$343 (CI: -$430 - -$257)
Costs for Prescription Drugs				
1st year	Base-case Analysis	$18,166	$8,945	$9,221
	Sensitivity Analysis	$18,135	$8,900	$9,235 (CI: $9,027 - $9,443)
2nd year	Base-case Analysis	$16,583	$13,371	$3,212
	Sensitivity Analysis	$16,638	$13,387	$3,251 (CI: $3,124 - $3,377)
3rd year	Base-case Analysis	$14,895	$12,895	$2,000
	Sensitivity Analysis	$14,911	$12,893	$2,017 (CI: $1,899 - $2,136)
Costs for Emergency Room Services				
1st year	Base-case Analysis	$574	$603	-$29
	Sensitivity Analysis	$571	$604	-$33 (CI: -$45 - -$22)
2nd year	Base-case Analysis	$478	$603	-$125
	Sensitivity Analysis	$471	$602	-$131 (CI: -$148 - -$114)
3rd year	Base-case Analysis	$388	$501	-$113
	Sensitivity Analysis	$399	$511	-$112 (CI: -$122 - -$103)

Sensitivity analysis results were based on the Monte Carlo simulation with 2000 iteration trials.

Appendix Table 7.3 Parameters for Sensitivity Analysis in Cost Analysis

Parameter	Base-case value	Distribution	Specification
Probability of a CD patient assessed with different disease severity in the 1st year after diagnosis	Remission: 0.236 Mild-mod.: 0.117 Mod.-sev.: 0.410 Sev./Fulm.: 0.237	Dirichlet	Dirichlet(236;117;410;237)
Total healthcare cost of a late biological user with different disease severity in the 1st year	Remission: $6,415 Mild-mod.: $16,416 Mod.-sev.: $23,336 Sev./Fulm.: $45,162	Gamma(κ, θ)	κ =0.362, θ=17,697 κ =0.838, θ=19,597 κ =1.156, θ=20,193 κ =1.267, θ=35,633
Total healthcare cost of a late biological user with different disease severity in the 2nd year	Remission: $10,660 Mild-mod.: $21,362 Mod.-sev.: $25,659 Sev./Fulm.: $46864	Gamma(κ, θ)	κ =0.498, θ=21,394 κ =0.645, θ=33,096 κ =1.644, θ=15,605 κ =1.115, θ=42,047
Transition probability of a late biological user with remission disease in the 1st year to different disease severity in the 2nd year	Remission: 0.265 Mild-mod.: 0.139 Mod.-sev.: 0.390 Sev./Fulm.: 0.206	Dirichlet	Dirichlet(265;139;390;206)
Transition probability of a late biological user with mild disease in the 1st year to different disease severity in the 2nd year	Remission: 0.171 Mild-mod.: 0.370 Mod.-sev.: 0.288 Sev./Fulm.: 0.171	Dirichlet	Dirichlet(171;370;288;171)
Transition probability of a late biological user with moderate disease in the 1st year to different disease severity in the 2nd year	Remission: 0.112 Mild-mod.: 0.077 Mod.-sev.: 0.639 Sev./Fulm.: 0.172	Dirichlet	Dirichlet(112;77;639;172)
Transition probability of a late biological user with severe disease in the 1st year to different disease severity in the 2nd year	Remission: 0.129 Mild-mod.: 0.123 Mod.-sev.: 0.366 Sev./Fulm.: 0.382	Dirichlet	Dirichlet(129;123;366;382)
Total healthcare cost of a early biological user with different disease severity in the 1st year	Remission: $24,904 Mild-mod.: $29,467 Mod.-sev.: $30,100 Sev./Fulm.: $47,444	Gamma(κ, θ)	κ =1.538, θ=16,190 κ =2.576, θ=11,440 κ =1.838, θ=16,381 κ =1.039, θ=45,683
Total healthcare cost of a early biological user with different disease severity in the 2nd year	Remission: $20,389 Mild-mod.: $24,316 Mod.-sev.: $30,051 Sev./Fulm.: $43,570	Gamma(κ, θ)	κ =1.164, θ=17,521 κ =1.580, θ=15,388 κ =1.532, θ=19,615 κ =1.154, θ=37,753

Parameter	Base-case value	Distribution	Specification
Transition probability of a early biological user with remission disease in the 1st year to different disease severity in the 2nd year	Remission: 0.690 Mild-mod.: 0.054 Mod.-sev.: 0.151 Sev./Fulm.: 0.105	Dirichlet	Dirichlet(690;54;151;105)
Transition probability of a early biological user with mild disease in the 1st year to different disease severity in the 2nd year	Remission: 0.289 Mild-mod.: 0.386 Mod.-sev.: 0.228 Sev./Fulm.: 0.097	Dirichlet	Dirichlet(289;386;228;97)
Transition probability of a early biological user with moderate disease in the 1st year to different disease severity in the 2nd year	Remission: 0.250 Mild-mod.: 0.074 Mod.-sev.: 0.549 Sev./Fulm.: 0.127	Dirichlet	Dirichlet(250;74;549;127)
Transition probability of a early biological user with severe disease in the 1st year to different disease severity s in the 2nd year	Remission: 0.297 Mild-mod.: 0.054 Mod.-sev.: 0.210 Sev./Fulm.: 0.439	Dirichlet	Dirichlet(297;54;210;439)

1.Parameters for Gamma distributions are approximated by mean and standard deviation: $\kappa = \bar{u}^2/s^2$, $\theta = s^2/\bar{u}$
2.Total healthcare costs in the 3rd year and transition probability from the 2nd to the 3rd year for both early and late biological users are similarly specified with Gamma and Dirichlet distributions. Meanwhile, costs of individual services (e.g. inpatient services) can also been similarly specified as total healthcare costs. Detailed specifications for those parameters are not included in the table above.

Appendix Table 7.4 Transition Probabilities of Frequent Biological Users

Year/Severity	Remission	Mild-moderate	Moderate-severe	Severe/Fulminant
Bottom-up biological users:				
1st year			2nd year	
Remission	0.207	0.069	0.534	0.190
Mild-moderate	0.120	0.333	0.344	0.203
Moderate-severe	0.094	0.059	0.669	0.177
Severe/Fulminant	0.145	0.101	0.347	0.407
2nd year			3rd year	
Remission	0.373	0.145	0.301	0.181
Mild-moderate	0.189	0.405	0.243	0.162
Moderate-severe	0.097	0.085	0.691	0.127
Severe/Fulminant	0.103	0.075	0.402	0.421
Top-down biological users:				
1st year			2nd year	
Remission	0.682	0.041	0.206	0.071
Mild-moderate	0.417	0.333	0.167	0.083
Moderate-severe	0.247	0.071	0.538	0.143
Severe/Fulminant	0.285	0.062	0.254	0.400
2nd year			3rd year	
Remission	0.603	0.078	0.233	0.086
Mild-moderate	0.143	0.286	0.357	0.214
Moderate-severe	0.164	0.073	0.618	0.145
Severe/Fulminant	0.195	0.001	0.267	0.537

Appendix Table 7.5 Total Healthcare Costs of Frequent Biological Users

Year/Severity	Remission	Mild-moderate	Moderate-severe	Severe/Fulminant
Bottom-up biological users:				
1st year	$6,063($9,203)	$14,859($17,814)	$24,246($24,320)	$43,565($31,833)
2nd year	$12,723($16,700)	$23,297($34,650)	$25,296($19,814)	$49,120($45,704)
3rd year	$17,978($20,007)	$22,365($27,248)	$25,456($22,218)	$41,592($41,382)
Top-down biological users:				
1st year	$25,218($22,090)	$37,633($20,463)	$30,234($21,089)	$50,055($44,453)
2nd year	$21,039($19,313)	$22,824($23,294)	$30,508($24,427)	$51,206($53,004)
3rd year	$14,630($15,254)	$18,106($15,557)	$31,086($36,393)	$41,666($33,898)

Mean and standard deviation, in parentheses, were calculated after adjusting to 2010 US$.
Only costs incurred in a full year were summarized.

Appendix Table 7.6 Characteristics of Biological Users with Crohn's Disease

Characteristics	Biological Users	Early Biological Users	Late Biological Users	Early Frequent Biological Users	Late Frequent Biological Users	P-value*
Total number of patients	6,068	3,082	2,986	848	1,556	
Year of disease diagnosis,%						<0.001
2005	920 (15.2%)	290 (9.4%)	630 (21.1%)	66 (7.8%)	293 (18.8%)	
2006	1,689 (27.8%)	1,038 (33.7%)	651 (21.8%)	269 (31.7%)	348 (22.4%)	
2007	916 (15.1%)	405 (13.1%)	511 (17.1%)	114 (13.4%)	275 (17.7%)	
2008	2,480 (40.9%)	1,321 (42.9%)	1,159 (38.8%)	392 (46.2%)	621 (39.9%)	
2009	63 (1.0%)	28 (0.9%)	35 (1.2%)	7 (0.8%)	19 (1.2%)	
Age at diagnosis, mean (SD)	37.9 (12.2)	38.0 (12.3)	37.7 (12.2)	37.4 (12.1)	37.9 (12.0)	0.332
Age at 40 years or above, %	2,609 (43.0%)	1,327 (43.1%)	1,282 (42.9%)	341 (40.2%)	684 (44.0%)	0.076
Female, %	3,281 (54.1%)	1,638 (53.1%)	1,643 (55.0%)	474 (55.9%)	851 (54.7%)	0.570
Diagnosed by GI specialist, %	1,846 (30.4%)	868 (28.2%)	978 (32.8%)	241 (28.4%)	531 (34.1%)	0.004
Region,%						0.085
Northeast	733 (12.1%)	365 (11.8%)	368 (12.3%)	109 (12.9%)	186 (12.0%)	
North Central	2,004 (33.0%)	1,102 (35.8%)	902 (30.2%)	287 (33.8%)	508 (32.6%)	
South	2,675 (44.1%)	1,336 (43.3%)	1,339 (44.8%)	375 (44.2%)	663 (42.6%)	
West, or unknown	656 (10.8%)	279 (9.0%)	377 (12.6%)	77 (9.0%)	199 (12.7%)	
MSA, %	5,221 (86.0%)	2,671 (86.7%)	2,550 (85.4%)	742 (87.5%)	1332 (85.6%)	0.197
Health Plan, %	3,440 (56.7%)	2,210 (71.7%)	1,230 (41.2%)	622 (73.3%)	650 (41.8%)	<0.001
PPO, %	4,487 (73.9%)	2,460 (79.8%)	2.027 (67.9%)	676 (79.7%)	1062 (68.3%)	<0.001
Fulltime employee, %	2,479 (40.9%)	833 (27.0%)	1,646 (55.1%)	223 (26.3%)	851 (54.7%)	<0.001
Non-dependent employee, %	3,824 (63.0%)	1,946 (63.1%)	1,878 (62.9%)	521 (61.4%)	1007 (64.7%)	0.111
CCI, mean (SD)	0.05 (0.28)	0.03 (0.22)	0.06 (0.33)	0.05 (0.25)	0.06 (0.28)	0.502
Rx prior to diagnosis, mean (SD)	1.61 (4.57)	0.55 (1.87)	2.71 (6.05)	0.58 (2.06)	3.18 (6.68)	<0.001

* P values were obtained from a Cochran-Mantel-Haenszel test for categorical variables (eg. year of diagnosis), and from a two-way ANOVA test for numerical variables (eg. age) while comparing the characteristics between early frequent biological users and late frequent biological users.

SD: standard deviation; MSA: metropolican statistical area; GI: gastroenterologist; PPO: preferred provider organization; CCI: Charlson comorbidity index

Appendix Table 7.7 Total Healthcare Costs and Inpatient Service Costs

Year/Severity	Remission	Mild-moderate	Moderate-severe	Severe/Fulminant
Inpatient Service Costs (unadjusted with any truncation)				
Late biological users:				
1st year	$1,226($5,045)	$1,006($4,355)	$2,208($13,585)	$20,768($31,489)
2nd year	$161($1,418)	$894($5,332)	$1,807($9,228)	$20,654($39,644)
3rd year	$292($2,437)	$1,855($9,594)	$1,993($11,004)	$18,076($31,946)
Early biological users:				
1st year	$648($3,911)	$306($2,691)	$1,896($7,544)	$20,218($38,887)
2nd year	$550($3,190)	$1,134($7,963)	$2,534($11,074)	$15,481($29,419)
3rd year	$329($1,917)	$1,050($4,150)	$6,365($70,352)	$15,661($29,917)
Inpatient Service Costs (with truncation at $500,000)				
Late biological users:				
1st year	$1,226($5,045)	$1,006($4,355)	$2,208($13,585)	$20,768($31,489)
2nd year	$161($1,418)	$894($5,332)	$1,807($9,228)	$20,614($39,144)
3rd year	$292($2,437)	$1,855($9,594)	$1,993($11,004)	$18,076($31,946)
Early biological users:				
1st year	$648($3,911)	$306($2,691)	$1,896($7,544)	$20,218($38,887)
2nd year	$550($3,190)	$1,134($7,963)	$2,534($11,074)	$15,481($29,419)
3rd year	$329($1,917)	$1,050($4,150)	$3,991($30,764)	$15,661($29,917)
Total Healthcare Costs (unadjusted with any truncation)				
Late biological users:				
1st year	$6,415($10,655)	$16,416($17,936)	$23,408($22,808)	$45,401($41,927)
2nd year	$10,660($15,102)	$21,362($26,589)	$25,659($20,010)	$47,655($50,457)
3rd year	$13,568($17,010)	$20,668($23,703)	$24,879($20,544)	$40,077($39,334)
Early biological users:				
1st year	$24,904($20,080)	$29,467($18,360)	$30,100($22,205)	$47,804($49,024)
2nd year	$20,389($18,901)	$24,316($19,344)	$30,051($24,278)	$43,570($40,557)
3rd year	$15,383($16,658)	$22,720($18,443)	$31,108($73,605)	$46,189($43,666)
Total Healthcare Costs (with truncation at $500,000)				
Late biological users:				
1st year	$6,415($10,655)	$16,416($17,936)	$23,408($22,808)	$45,401($41,927)
2nd year	$10,660($15,102)	$21,362($26,589)	$25,659($20,010)	$47,615($50,053)
3rd year	$13,568($17,010)	$20,668($23,703)	$24,879($20,544)	$40,077($39,334)
Early biological users:				
1st year	$24,904($20,080)	$29,467($18,360)	$30,100($22,205)	$47,804($49,024)
2nd year	$20,389($18,901)	$24,316($19,344)	$30,051($24,278)	$43,570($40,557)
3rd year	$15,383($16,658)	$22,720($18,443)	$28,734($36,823)	$46,189($43,666)

Mean and standard deviation, in parentheses, were calculated after adjusting to 2010 US$.
Only costs incurred in a full year were summarized.

Appendix Table 7.8 Comparison of Total Healthcare Costs and Inpatient Service Costs

Year	Analysis	Top-down Biological User	Bottom-up Biological User	Difference
Inpatient Service Costs (based on unadjusted cost data)				
1st year	Base-case Analysis	$5,757	$6,234	-$477
	Sensitivity Analysis	$5,798	$6,269	-$471 (CI: -$577 - -$365)
2nd year	Base-case Analysis	$4,148	$5,561	-$1,413
	Sensitivity Analysis	$4,308	$5,718	-$1,410 (CI: -$1,609 - -$1,211)
3rd year	Base-case Analysis	$5,487	$4,986	$693
	Sensitivity Analysis	$5,564	$5,070	$493 (CI: $332 - $655)
Inpatient Service Costs (based on cost data truncated at $500,000)				
1st year	Base-case Analysis	$5,672	$6,234	-$477
	Sensitivity Analysis	$5,798	$6,269	-$471 (CI: -$577 - -$365)
2nd year	Base-case Analysis	$4,148	$5,552	-$1,404
	Sensitivity Analysis	$4,257	$5,623	-$1,367 (CI: -$1,571 - -$1,162)
3rd year	Base-case Analysis	$4,610	$4,986	-$376
	Sensitivity Analysis	$4,705	$5,104	-$400 (CI: -$548 - -$252)
Total Healthcare Costs (based on unadjusted cost data)				
1st year	Base-case Analysis	$32,995	$23,792	$9,203
	Sensitivity Analysis	$33,075	$23,597	$9,478 (CI: $9,122 - $9,833)
2nd year	Base-case Analysis	$28,500	$27,536	$964
	Sensitivity Analysis	$28,189	$27,079	$1,110 (CI: $819 - $1,401)
3rd year	Base-case Analysis	$27,578	$25,608	$1,970
	Sensitivity Analysis	$28,094	$25,778	$2,316 (CI: $2,060 - $2,571)
Total Healthcare Costs (based on cost data truncated at $500,000)				
1st year	Base-case Analysis	$32,995	$23,792	$9,203
	Sensitivity Analysis	$33,075	$23,597	$9,478 (CI: $9,122 - $9,833)
2nd year	Base-case Analysis	$28,500	$27,527	$973
	Sensitivity Analysis	$28,352	$27,557	$796 (CI: $506 - $1,085)
3rd year	Base-case Analysis	$26,701	$25,608	$1,093
	Sensitivity Analysis	$26,677	$25,501	$1,176 (CI: $927 - $1,425)

Sensitivity analysis results were based on the Monte Carlo simulation with 2000 iteration trials.

CHAPTER VIII:

STUDY FINDINGS AND LIMITATIONS

8.1 Summary of Findings

This dissertation sought to evaluate the economic consequences on payers when the treatment paradigm for Crohn's disease(CD) management is shifting from the conventional and conservative algorithm to a more aggressive treatment strategy. We examined healthcare utilization and costs for CD patients in a large claims database from 2005 to 2009. Specifically, we compared CD patients who used novel biological therapies following two alternate treatment strategies, 'top-down' and 'bottom-up' approaches. The top-down approach endorses early use of biological therapy in initial treatment, and bottom-up approach promotes late use of biological therapy after non-biological medical treatments have been attempted. Based on empirical data for CD patients, we constructed decision tree models to predict the differences in annual costs of prescription drugs and total healthcare services in the first three years of CD between patients who use the top-down or bottom-up strategy in disease management. To our knowledge, this study is the first to use real-world data to demonstrate the financial implications to payers resulting from the shift in CD treatment strategy.

In Chapter V, we reported that biological therapies have been increasingly used among CD patients in recent years. From comparisons of healthcare utilization between early and late biological adopters, we found that both groups of CD patients used a similar amount of outpatient services. However, early biological adopters used less inpatient and emergency room services, and incurred few expenses for both services. Early adopter also filled a fewer number of prescriptions, but had greater drug costs because biological therapies are more expensive. Average total healthcare costs per year paid by third party payers were not categorically different between early and late biological users from 2005 to 2009. These results indicate that the new and more aggressive treatment strategy did not cause a rapid increase in overall healthcare costs for CD patients. Further, we compared a broad range of patient and provider characteristics between the two CD patient cohorts, and found great similarities. For example, both early and late biological users were at similar age at diagnosis, gender distribution, urban residence, and provider specialty. We also noticed these two groups differed in socioeconomic status (e.g., employment status) and general health condition (e.g., comorbidity and prescription use). Multivariate regression models confirmed that these variables played a significant role in predicting healthcare utilization and costs between the two user groups. Due to lack of detailed information about patient socioeconomic information and general health assessment in the source data, it is likely that relevant variables were omitted in the analyses. Despite statistical adjustments in the multivariable regression models, selection bias could have been introduced into the study sample and cohort definition. Therefore, the findings in Chapter 5 were informative rather than conclusive.

In Chapter VI, a decision tree model was constructed where top-down approach was the base case scenario and bottom-up therapy was the alternative. The model was used to predict annual prescription drug costs in the first, second, and third years of disease for patients. In the decision tree, disease severity was the model for possible outcomes of CD treatment. At each chance node on the decision tree, four separate disease severity categories (i.e., remission, mild to moderate, moderate to severe, and severe or fulminant) were used to classify patients by symptoms and healthcare utilization records. Based on the decision tree model, budget impact analyses were performed from the perspective of Pharmacy Benefit Management Organizations (PBMOs) with all model parameters (including costs and probabilities) estimated from the claims data. We found that the top-down strategy resulted in a substantial increase in prescription drug costs during patients' first year of CD. The difference in prescription drug costs was reduced significantly in the second and third years of disease. These important findings provide key messages to payers, particularly PBMOs. The treatment strategy shift from bottom-up to top-down approach of biological therapy would result in a drastic increase in prescription drug costs in the first year of disease, but extra drug costs associated with this treatment strategy shift are much lower in the second and third years. Within a three-year time frame, it is evident that the treatment strategy shift towards the early, more aggressive algorithm would not impose a severe financial burden for payers. However, caution needs to be practiced when extrapolating these findings over a longer time period. The large difference in drug costs in the first year of disease between patients using the two treatment strategies was primarily attributable to the timing of initial biological treatment. Whereas top-down user began their first biological treatment, on average, three months after diagnosis, bottom-up adopters used their first biotherapy one year

after diagnosis. We found that prescription drug costs for top-down users were 15 - 20% higher during the first and second years of disease than costs for bottom-up users during the same time period. It is unknown if the increase in annual drug costs would titrate over time. The top-down strategy might require a long-term budgetary increase for MCOs since CD is lifelong for most patients. The decision tree model predicted that CD patients using the top-down approach were less likely to have severe disease at the end of three years . This is an indicator that early adoption of biotherapies resulted in better clinical outcomes, and could subsequently affect patients' utilization of healthcare services.

In Chapter VII, a cost analysis was conducted to compare a broader scope of healthcare costs between patients in the base case (bottom-up approach) and those in the alternate case (top-down approach) scenario. We used the same decision model from Chapter VI, but expanded costs to include prescription drugs, total healthcare services, and more specific services, including inpatient, outpatient, and emergency room services. We found that CD patients who followed top-down approach incurred substantially higher costs for total healthcare services in the first year of disease. This increase in healthcare costs was mainly driven by the difference in the induction time of biological therapies between patients using top-down or bottom-up approach. The incremental costs of total healthcare services for top-down biological users was significantly reduced in the second and third years of disease. The top-down treatment strategy also resulted in long-term cost neutrality as the healthcare costs for CD patients became comparable with those costs for bottom-up users over time.

We further examined healthcare costs according to the types of services that CD patients received, which were grouped into four categories: a) inpatient services; b) outpatient services; c) emergency room services; and d) prescription drugs. We found that the

convergence of total healthcare costs for CD patients could be explained by a cost shift between drug and non-drug services (i.e., inpatient, outpatient, and emergency room services). Even though prescription drug costs for top-down users remained elevated and were higher than drug costs for bottom-up users in the third year of disease, top-down users' costs for outpatient, inpatient, and emergency room services were lower. In addition, we conducted subgroup analyses among CD patients who used biological therapies more aggressively and persistently after the initial dose of biotherapy. A financial savings was achieved in the third year of disease for patients who followed top-down strategy and used three or more doses (including the initial dose) of biological therapies in the three months following their initial biological dose. Our results suggested that better compliance to biological therapies could result in improved economic outcomes and reduced healthcare costs for third party payers.

In summary, this dissertation showed that novel biological therapies have been increasingly used among CD patients, and their choice of treatment strategy can affect healthcare costs. From the perspective of third party payers, the new and aggressive top-down treatment approach incurred higher prescription drug costs than the conventional bottom-up treatment strategy, especially in the first year of disease. The top-down treatment strategy for CD is projected to be cost neutral because patients incur lower costs for non-drug services in the long term. In comparison with the top-down treatment strategy, the bottom-up treatment strategy is associated with a 270-day deferral of use of biological therapies. The short-term cost reduction of the bottom-up users in the first year of disease cannot be converted to a long-term cost saving. On the contrary, the bottom-up treatment strategy can lead to worsening clinical outcomes and increased non-drug healthcare costs. Therefore, it is

recommended that payers to balance their short-term budget to include more pharmacy-related benefits and their long-term budget to encompass other medical benefits. Restricting early access to biological therapies is unnecessary since the top-down treatment approach does not incur greater costs than the bottom-up strategy over time.

8.2 Limitations

Data Issues

Despite the merits of a large claims database in observational studies, there were some drawbacks to using the MarketScan Commercial Claims and Encounter (CCAE) database as the primary data source in this dissertation. The limitations of this real-world data can potentially threaten the internal and external validity of our study results. Therefore, caution needs to be practiced when interpreting our findings.

In this dissertation, we selected patients diagnosed with Crohn's disease who filed claims between 2005 and 2009. These patients were between 18 and 64 years old with commercial insurance coverage, and comprised the majority of enrollees in the MarketScan CCAE database. Older patients aged 65 and above were mostly retirees, and eligible for Medicare. A large portion of young patients under age 18 were insured by public insurance programs (e.g., Medicaid and SCHIP). Therefore, our findings may not be generalizable to patients aged 65 and above and under 18 years, even though CD can affect both.[16]

The MarketScan database provides rich information about patients' utilization records from pharmacy counters or other medical facilities whenever a claim is filed to an insurer. When serving as source data for an observational study, the MarketScan database lacks personal information about each patient's demographic and socioeconomic status as well as

detailed medical and clinical data. When developing the conceptual framework for this study, we recognized that education level, annual income, and race were important factors that could potentially impact a patient's choice of treatment strategy. Omitting these variables in the analytical models could have introduced selection bias into comparisons of healthcare utilization and costs between the two patient cohorts.

We also realized that more accurate information about patients' initial diagnosis of CD, general health condition, and progression of disease severity was needed to ensure the credibility of our study findings. Unfortunately, the MarketScan database does not contain detailed clinical and medical histories, so other measurements were developed to approximate those variables. For example, we denoted the CD diagnosis date as the date of the first claim for a procedure with a CD diagnosis or a prescription for a CD drug. We assumed that patients were newly diagnosed with CD if no CD-related claims were filed in the six months preceding the diagnosis. We used the Charlson Comorbidity Scores and the number of prescriptions filled in six months prior to diagnosis to approximate the general health condition at diagnosis. Further, we used a claims-based algorithm developed by Malone et al. to define disease severity. This method was considered as a better proxy for disease severity classification compared to other algorithms because it reflects the current treatment practice in the US. However, this claims-based approach has not been verified in an actual patient population. It is unknown how accurate the definition of disease severity is when compared with standard way in clinical practice. There is likely a potential misclassification, particularly for patients with milder disease symptom and patients who under-utilized healthcare services. [68]

Modeling Issues

A decision tree is a simple and effective form of a decision model. In this dissertation, the budget impact analysis for Aim 2 and cost analysis for Aim 3 were based on the same decision tree model. Since we took a real-world data approach to predict the incremental costs of the new treatment strategy (early adoption), the time frame for the decision tree model was set to three years, which was based on availability of claims data for CD patients in the MarketScan database. In order to obtain consistent estimates of healthcare costs (payoff value) and probabilities at each chance node, we required at least 20 patients in the same path for each year of either treatment scenario. From our study cohorts (3,082 early biological users and 2,986 late biological users), we could not identify an adequate number of patients to empirically estimate model parameters for the fourth year of disease. For example, among 26 early biological users with mild to moderate disease in the third year of CD, there were 6 patients had mild disease and only 1 patient had severe disease in the fourth year. Sample sizes reduction over time due to attrition prevented us from extending the time frame of the decision model. Based on the three-year decision tree model, the budget impact analysis for Aim 2 and cost analysis for Aim 3 provided positive information about the value of biological therapies for CD patients, and the tendency toward financial benefits under the new treatment strategy. However, a time frame of 5-10 years would be more desirable to demonstrate the long-term value of the new treatment strategy since CD is chronic.

Another major methodological issue should be mentioned. The budget impact and cost analyses were not the best economic evaluation methods to effectively demonstrate the value of a new treatment or technology since both methods focus on costs rather than effectiveness (namely, health-related quality of life). In the decision tree model, disease

severity was designated as an outcome of medical treatment. Change in disease severity (either improving or worsening) may be correlated to patients' quality of life. However, disease severity, often in discreet categories, cannot quantitatively represent quality of life on a continuous numeric scale. To account for both costs and effectiveness, cost-effectiveness analysis (CEA) is a more appropriate method for economic evaluation. However, lack of effectiveness data was the obvious barrier to using CEA. The MarketScan database does not contain information about health related quality of life. In the literature, quality of life data were only reported in randomized clinical trials (RCTs) according to treatment arms. Without patient- level information, the published RCT data cannot be incorporated into the decision tree model where patients were stratified by disease severity. Furthermore, RCT data were obtained from studies with relatively small sample sizes, so the results may not be generalizable to a large patient population.

8.3 Future Research Directions

The study findings and limitations above suggest directions for future research. First, to improve the budget impact analysis and cost-analysis models in predicting the long-term financial effect of the new treatment strategy, we will need to construct the decision model based on a longer time frame, preferably five years. To overcome the constraint on sample size, it is recommended that future studies include claims data from more recent years once they become available. For the analyses in this study, the most recent year of the MarketScan data was 2009. Claims data from 2010 and 2011 could expand the sample size substantially, and extend the follow-up time for more patients. We could also consider combining the

MarketScan database with another commercial claims database, such as PharMetrics, to further increase the sample size. Both MarketScan and PharMetrics include claims data for a similar patient population and have similar data structure. Although some patient data may be included in both databases, the combined source data would provide a larger patient pool, and allow us extend the time frame to five years or beyond to demonstrate the long-term effect of the new treatment strategy on CD patients.

Second, we recommend that investigators conduct future research with an older patient population to evaluate the financial implications of treatment strategy change for CD management. CD in older people (aged 60 and above) counts for 10%-15% of cases of the disease and significantly amount of hospitalizations, [97] and healthcare costs for older CD patients are believed to be elevated for payers, mainly Medicare. Compared to younger CD patients, older patients have more comorbid conditions, different socioeconomic status (e.g., most are retirees), and homogenous health insurance coverage. Therefore, the effect of the treatment strategy shift from the late to early adoption on the older patient population is likely different from the findings in this dissertation.

Third, sub-group analyses are recommended to address more specific research questions under certain scenarios. In the economic evaluation in this dissertation, we combined all biological agents into one drug therapy without taking into account of heterogeneity of treatment effect from individual agent. Future studies can be designed to estimate the healthcare costs for patients who use one of biological agents or switch to another biological agents due to intolerance or non-response to the initial biological agent.

Last but not least, future studies need to be conducted in the framework of CEA or CUA. To show the value of novel biological therapies adopted using different treatment

strategies, CEA is an appropriate method since it accounts for both costs and effects associated with alternative strategies. Lack of patient-level data reflecting quality of life will be a challenge when implementing CEA, and it may be necessary to use simulated data based on previously published studies. Under the framework of CUA, it would be meaningful for payers if we can estimate the annual costs per unit change of disease severity (e.g., from moderate-severe to mild-moderate disease) when a patient follows either the top-down or bottom-up treatment strategy.

In conclusion, this dissertation found that CD treatment strategy shift from the bottom-up to top-down approach will not increase prescription drug costs and total healthcare costs for payers in a long term. Future studies are recommended to continue to evaluate these novel biological therapies from a broader perspective, and in a greater depth when more research data become available.

REFERENCES

1. Loftus, E.V., Jr., et al., *Long-term fracture risk in patients with Crohn's disease: a population-based study in Olmsted County, Minnesota.* Gastroenterology, 2002. **123**(2): p. 468-75.
2. Silverstein, M.D., et al., *Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort.* Gastroenterology, 1999. **117**(1): p. 49-57.
3. Yu, A.P., et al., *The costs of Crohn's disease in the United States and other Western countries: a systematic review.* Curr Med Res Opin, 2008. **24**(2): p. 319-28.
4. Hay, J.W. and A.R. Hay, *Inflammatory bowel disease: costs-of-illness.* J Clin Gastroenterol, 1992. **14**(4): p. 309-17.
5. Feagan, B.G., et al., *Annual cost of care for Crohn's disease: a payor perspective.* Am J Gastroenterol, 2000. **95**(8): p. 1955-60.
6. Kappelman, M.D., et al., *Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults.* Gastroenterology, 2008. **135**(6): p. 1907-13.
7. Hanauer, S.B., et al., *Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial.* Lancet, 2002. **359**(9317): p. 1541-9.
8. Colombel, J.F., et al., *Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial.* Gastroenterology, 2007. **132**(1): p. 52-65.
9. Schreiber, S., et al., *Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data.* Am J Gastroenterol, 2010. **105**(7): p. 1574-82.
10. Cohen, R.D., *Inflammatory Bowel Disease Diagnosis and Therapeutics*. Second ed. 2003: Humana Press.
11. Lichtenstein, G.R., S.B. Hanauer, and W.J. Sandborn, *Management of Crohn's disease in adults.* Am J Gastroenterol, 2009. **104**(2): p. 465-83; quiz 464, 484.
12. Colombel, J.F., *Understanding combination therapy with biologics and immunosuppressives for the treatment of Crohn's disease.* Gastroenterol Hepatol (N Y), 2010. **6**(8): p. 486-90.
13. D'Haens, G.R., et al., *Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial.* Gastroenterology, 2008. **135**(4): p. 1123-9.

14. Hoadley, J., *Cost Containment Strategies For Prescription Drugs: Assessing The Evidence In The Literature*. 2005, The Kaiser Family Foundation.

15. Loftus, E.V., Jr., et al., *Cost-effectiveness of adalimumab for the maintenance of remission in patients with Crohn's disease.* Eur J Gastroenterol Hepatol, 2009. **21**(11): p. 1302-9.

16. Loftus, E.V., Jr., et al., *Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival.* Gastroenterology, 1998. **114**(6): p. 1161-8.

17. Mendeloff, A.I., *The epidemiology of inflammatory bowel disease.* Clin Gastroenterol, 1980. **9**(2): p. 259-70.

18. Bernstein, C.N. and J.F. Blanchard, *The epidemiology of Crohn's disease.* Gastroenterology, 1999. **116**(6): p. 1503-4.

19. Silverstein, M.D., et al., *Cigarette smoking in Crohn's disease.* Am J Gastroenterol, 1989. **84**(1): p. 31-3.

20. Farrell, R.J., *Crohn's disease: not all anti-TNFs are the same!* Inflamm Bowel Dis, 2002. **8**(3): p. 232-3.

21. Langholz, E., *Current trends in inflammatory bowel disease: the natural history.* Therap Adv Gastroenterol, 2010. **3**(2): p. 77-86.

22. Canavan, C., K.R. Abrams, and J.F. Mayberry, *Meta-analysis: mortality in Crohn's disease.* Aliment Pharmacol Ther, 2007. **25**(8): p. 861-70.

23. Ljung, T., et al., *Infliximab in inflammatory bowel disease: clinical outcome in a population based cohort from Stockholm County.* Gut, 2004. **53**(6): p. 849-53.

24. Colombel, J.F., et al., *Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy.* Am J Gastroenterol, 2004. **99**(5): p. 878-83.

25. Faubion, W.A., Jr., et al., *The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study.* Gastroenterology, 2001. **121**(2): p. 255-60.

26. Munkholm, P., *Crohn's disease--occurrence, course and prognosis. An epidemiologic cohort-study.* Dan Med Bull, 1997. **44**(3): p. 287-302.

27. Ho, G.T., et al., *The efficacy of corticosteroid therapy in inflammatory bowel disease: analysis of a 5-year UK inception cohort.* Aliment Pharmacol Ther, 2006. **24**(2): p. 319-30.

28. Burdmann, E.A., et al., *Cyclosporine nephrotoxicity.* Semin Nephrol, 2003. **23**(5): p. 465-76.

29. Sandborn, W.J., B.G. Feagan, and G.R. Lichtenstein, *Medical management of mild to moderate Crohn's disease: evidence-based treatment algorithms for induction and maintenance of remission.* Aliment Pharmacol Ther, 2007. **26**(7): p. 987-1003.

30. Katz, J.A., *Advances in the medical therapy of inflammatory bowel disease.* Curr Opin Gastroenterol, 2002. **18**(4): p. 435-40.

31. Xavier, R.J. and D.K. Podolsky, *Unravelling the pathogenesis of inflammatory bowel disease.* Nature, 2007. **448**(7152): p. 427-34.

32. Bai, A. and Z. Peng, *Biological therapies of inflammatory bowel disease.* Immunotherapy, 2010. **2**(5): p. 727-42.

33. Oldenburg, B. and D. Hommes, *Biological therapies in inflammatory bowel disease: top-down or bottom-up?* Curr Opin Gastroenterol, 2007. **23**(4): p. 395-9.

34. Hartman, M., et al., *Health spending growth at a historic low in 2008.* Health Aff (Millwood), 2010. **29**(1): p. 147-55.

35. Yu, A.P., et al., *Cost utility of adalimumab versus infliximab maintenance therapies in the United States for moderately to severely active Crohn's disease.* Pharmacoeconomics, 2009. **27**(7): p. 609-21.

36. Rubenstein, J.H., R.Y. Chong, and R.D. Cohen, *Infliximab decreases resource use among patients with Crohn's disease.* J Clin Gastroenterol, 2002. **35**(2): p. 151-6.

37. Hanauer, S.B., *Positioning biologic agents in the treatment of Crohn's disease.* Inflamm Bowel Dis, 2009. **15**(10): p. 1570-82.

38. Hilsden, R.J., et al., *A national survey on the patterns of treatment of inflammatory bowel disease in Canada.* BMC Gastroenterol, 2003. **3**: p. 10.

39. Jewell, D.P., et al., *Infliximab use in Crohn's disease: impact on health care resources in the UK.* Eur J Gastroenterol Hepatol, 2005. **17**(10): p. 1047-52.

40. Pressman, A.R., et al., *Patterns of infliximab use among Crohn's disease patients in a community setting.* Inflamm Bowel Dis, 2008. **14**(9): p. 1265-72.

41. Feagins, L.A. and S.J. Spechler, *Biologic agent use varies inversely with age at diagnosis in Crohn's disease.* Dig Dis Sci, 2010. **55**(11): p. 3164-70.

42. Gibson, T.B., et al., *The direct and indirect cost burden of Crohn's disease and ulcerative colitis.* J Occup Environ Med, 2008. **50**(11): p. 1261-72.

43. Ollendorf, D.A. and L. Lidsky, *Infliximab drug and infusion costs among patients with Crohn's disease in a commercially-insured setting.* Am J Ther, 2006. **13**(6): p. 502-6.

44. Kane, S.V., J. Chao, and P.M. Mulani, *Adherence to infliximab maintenance therapy and health care utilization and costs by Crohn's disease patients.* Adv Ther, 2009. **26**(10): p. 936-46.

45. Sandborn, W.J., et al., *Dosage adjustment during long-term adalimumab treatment for Crohn's disease: clinical efficacy and pharmacoeconomics.* Inflamm Bowel Dis, 2011. **17**(1): p. 141-51.

46. Kappelman, M.D., et al., *Utilization of healthcare resources by U.S. children and adults with inflammatory bowel disease.* Inflamm Bowel Dis, 2010. **17**(1): p. 62-8.

47. Nugent, Z., J.F. Blanchard, and C.N. Bernstein, *A population-based study of health-care resource use among infliximab users.* Am J Gastroenterol, 2009. **105**(9): p. 2009-16.

48. Blomqvist, P., et al., *A 10-year survey of inflammatory bowel diseases-drug therapy, costs and adverse reactions.* Aliment Pharmacol Ther, 2001. **15**(4): p. 475-81.

49. Neumann, P.J. and S.D. Sullivan, *Economic evaluation in the US: what is the missing link?* Pharmacoeconomics, 2006. **24**(11): p. 1163-8.

50. Arseneau, K.O., et al., *Cost-utility of initial medical management for Crohn's disease perianal fistulae.* Gastroenterology, 2001. **120**(7): p. 1640-56.

51. Clark, W., et al., *Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.* Health Technol Assess, 2003. **7**(3): p. 1-67.

52. Jaisson-Hot, I., et al., *Management for severe Crohn's disease: a lifetime cost-utility analysis.* Int J Technol Assess Health Care, 2004. **20**(3): p. 274-9.

53. Lindsay, J., et al., *Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease--modelling outcomes in active luminal and fistulizing disease in adults.* Aliment Pharmacol Ther, 2008. **28**(1): p. 76-87.

54. Bodger, K., T. Kikuchi, and D. Hughes, *Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data.* Aliment Pharmacol Ther, 2009. **30**(3): p. 265-74.

55. Kaplan, G.G., et al., *Infliximab dose escalation vs. initiation of adalimumab for loss of response in Crohn's disease: a cost-effectiveness analysis.* Aliment Pharmacol Ther, 2007. **26**(11-12): p. 1509-20.

56. Gold MR, S.J., Russell LB, Weinstein MC, *Cost-Effectiveness in Health and Medicine*. 1996: Oxford University Press.

57. Mauskopf, J.A., et al., *Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis.* Value Health, 2007. **10**(5): p. 336-47.

58. Sorensen, J. and L.S. Andersen, *The case of tumour necrosis factor-alpha inhibitors in the treatment of rheumatoid arthritis: a budget impact analysis.* Pharmacoeconomics, 2005. **23**(3): p. 289-98.

59. Saro, C., et al., *Resource use in patients with Crohn's disease treated with infliximab.* Aliment Pharmacol Ther, 2007. **26**(10): p. 1313-23.

60. Andersen, R.M., *Revisiting the behavioral model and access to medical care: does it matter?* J Health Soc Behav, 1995. **36**(1): p. 1-10.

61. Grossman, M., *On the Concept of Health Capital and the Demand for Health.* Journal of Political Economy, 1972. **80**(2): p. 223-255.

62. Muurinen, J.M., *Demand for health: a generalised Grossman model.* J Health Econ, 1982. **1**(1): p. 5-28.

63. Schwartz, K.H., Jhamirah, *Health Insurance coverage of America's children*. 2009, The Kaiser Family Foundataion.

64. Zeger, S.L. and K.Y. Liang, *Longitudinal data analysis for discrete and continuous outcomes.* Biometrics, 1986. **42**(1): p. 121-30.

65. Horton, W.E., Jr., et al., *An association between an aggrecan polymorphic allele and bilateral hand osteoarthritis in elderly white men: data from the Baltimore Longitudinal Study of Aging (BLSA).* Osteoarthritis Cartilage, 1998. **6**(4): p. 245-51.

66. Park, T., D.W. Shin, and C.G. Park, *A generalized estimating equations approach for testing ordered group effects with repeated measurements.* Biometrics, 1998. **54**(4): p. 1645-53.

67. Stern, D. and D. Reissman, *Specialty pharmacy cost management strategies of private health care payers.* J Manag Care Pharm, 2006. **12**(9): p. 736-44.

68. Malone, D.C., et al., *A claims-based Markov model for Crohn's disease.* Aliment Pharmacol Ther, 2010. **32**(3): p. 448-58.

69. Hanauer, S.B. and W. Sandborn, *Management of Crohn's disease in adults.* Am J Gastroenterol, 2001. **96**(3): p. 635-43.

70. US Bureau of Labor Statistics.. *Consumer Price Index Archived News Releases*. [cited August 10, 2011]; Available from: http://www.bls.gov/schedule/archives/cpi_nr.htm#2010.

71. Briggs, A., K. Claxton, and M. Sculper, *Decision Modelling for Health Economic Evaluation*. 2006: Oxford University Press.

72. Briggs, A.H., A.E. Ades, and M.J. Price, *Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework.* Med Decis Making, 2003. **23**(4): p. 341-50.

73. Katz, J.A., *Treatment of inflammatory bowel disease with corticosteroids.* Gastroenterol Clin North Am, 2004. **33**(2): p. 171-89, vii.

74. Park, K.T. and D. Bass, *Inflammatory bowel disease-attributable costs and cost-effective strategies in the United States: a review.* Inflamm Bowel Dis, 2011. **17**(7): p. 1603-9.

75. Ray, W.A., *Evaluating medication effects outside of clinical trials: new-user designs.* Am J Epidemiol, 2003. **158**(9): p. 915-20.

76. de Boer, A.G., W. Wijker, and H.C. de Haes, *Predictors of health care utilization in the chronically ill: a review of the literature.* Health Policy, 1997. **42**(2): p. 101-15.

77. Deyo, R.A., D.C. Cherkin, and M.A. Ciol, *Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases.* J Clin Epidemiol, 1992. **45**(6): p. 613-9.

78. Mays, G.P., G. Claxton, and J. White, *Managed care rebound? Recent changes in health plans' cost containment strategies.* Health Aff (Millwood), 2004. **Suppl Web Exclusives**: p. W4-427-36.

79. Liang, S.Y., J.S. Haas, and K.A. Phillips, *Medicare formulary coverage for top-selling biologics.* Nat Biotechnol, 2009. **27**(12): p. 1082-4.

80. Yamamoto, D., *How Does the Benefit Value of Medicare Compare to the Benefit Value of Typical Large Employer Plans?* Medicare Issue Brief, Kaiser Family Foundation, 2008.

81. Gruber, J. and L. Levitt, *Tax subsidies for health insurance: costs and benefits.* Health Aff (Millwood), 2000. **19**(1): p. 72-85.

82. Eibner, C., *Employers' health insurance cost burden, 1996-2005.* Monthly Labor Review, 2008. **131**(6): p. 28-44.

83. Burger, D. and S. Travis, *Conventional medical management of inflammatory bowel disease.* Gastroenterology, 2011. **140**(6): p. 1827-1837 e2.

84. Sands, B.E., et al., *Maintenance infliximab does not result in increased abscess development in fistulizing Crohn's disease: results from the ACCENT II study.* Aliment Pharmacol Ther, 2006. **23**(8): p. 1127-36.

85. Sandborn, W.J., et al., *Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial.* Gut, 2007. **56**(9): p. 1232-9.

86. URAC. *Pharmacy Benefit Management*. [cited 2012 January 10]; Available from: https://ww.urac.org/resources/pharmacyBenefitManagement.aspx.

87. Jones, J.D., *How MCOs can get optimal value from their pharmacy benefit managers.* Manag Care, 2008. **17**(5): p. 43-5.

88. Navarro, R. and R. Hailey, *Overview of Prescription Drug Benefits in Managed Care*. p. 17.

89. Serono, *Serono Injectables Digest, 2nd edition*. 2006: Rockland, MA.

90. Baumgart, D.C. and S.R. Carding, *Inflammatory bowel disease: cause and immunobiology.* Lancet, 2007. **369**(9573): p. 1627-40.

91. CBO, *Evidence on the Costs and Benefits of Health Information Technology, A CBO Paper*. 2008.

92. Flood, J., et al., *The use of therapeutic interchange for biologic therapies.* Manag Care, 2007. **16**(1): p. 51-62.

93. Taylor, K.M. and P.M. Irving, *Optimization of conventional therapy in patients with IBD.* Nat Rev Gastroenterol Hepatol, 2011. **8**(11): p. 646-56.

94. Goldberg, E.L., et al., *Patient medication adherence: the forgotten aspect of biologics.* Biotechnol Healthc, 2009. **6**(2): p. 39-44.

95. Blum, M.A., D. Koo, and J.A. Doshi, *Measurement and rates of persistence with and adherence to biologics for rheumatoid arthritis: a systematic review.* Clin Ther, 2011. **33**(7): p. 901-13.

96. Magro, F. and F. Portela, *Management of inflammatory bowel disease with infliximab and other anti-tumor necrosis factor alpha therapies.* BioDrugs, 2010. **24 Suppl 1**: p. 3-14.

97. del Val, J.H., *Old-age inflammatory bowel disease onset: a different problem?* World J Gastroenterol, 2011. **17**(22): p. 2734-9.